TITLE OF THE INVENTION

OMEGA-CONOPEPTIDES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims benefit under 35 USC §119(e) to U.S. provisional patent applications Serial No. 60/219,616 filed on 21 July 2000 and Serial No. 60/265,888 filed on 5 February 2001. Each of these applications are incorporated herein by reference.

[0002] This invention was made with Government support under Grant No. PO1 GM48677 awarded by the National Institute of General Medical Sciences, National Institutes of Health, Bethesda, Maryland. The United States Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] The invention relates to ω-conopeptides, derivatives or pharmaceutically acceptable salts thereof, and uses thereof, including the treatment of neurologic and psychiatric disorders, such as anticonvulsant agents, as neuroprotective agents, as cardiovascular agents or for the management of pain. The invention further relates to nucleic acid sequences encoding the conopeptides and encoding propeptides, as well as the propeptides.

[0004] The publications and other materials used herein to illuminate the background of the invention, and in particular, cases to provide additional details respecting the practice, are incorporated by reference, and for convenience are referenced in the following text by author and date and are listed alphabetically by author in the appended bibliography.

[0005] *Conus* is a genus of predatory marine gastropods (snails) which envenomate their prey. Venomous cone snails use a highly developed projectile apparatus to deliver their cocktail of toxic conotoxins into their prey. In fish-eating species such as *Conus magus* the cone detects the presence of the fish using chemosensors in its siphon and when close enough extends its proboscis and fires a hollow harpoon-like tooth containing venom into the fish. This immobilizes the fish and enables the cone snail to wind it into its mouth via an attached filament. For general information on *Conus* and their venom see the website address http://grimwade.biochem.unimelb.edu.au/cone/referenc.html. Prey capture is accomplished through a sophisticated arsenal of peptides which target specific ion channel and receptor subtypes. Each *Conus* species venom appears to contain a unique set of 50-200 peptides. The composition of the venom differs greatly between species and between individual snails within

each species, each optimally evolved to paralyse it's prey. The active components of the venom are small peptides toxins, typically 12-30 amino acid residues in length and are typically highly constrained peptides due to their high density of disulphide bonds.

[0006] The venoms consist of a large number of different peptide components that when separated exhibit a range of biological activities: when injected into mice they elicit a range of physiological responses from shaking to depression. The paralytic components of the venom that have been the focus of recent investigation are the α-, ω- and μ-conotoxins. All of these conotoxins act by preventing neuronal communication, but each targets a different aspect of the process to achieve this. The α-conotoxins target nicotinic ligand gated channels, the μ-conotoxins target the voltage-gated sodium channels and the ω-conotoxins target the voltage-gated calcium channels (Olivera et al., 1985; Olivera et al., 1990). For example a linkage has been established between α-, αA- & ϕ-conotoxins and the nicotinic ligand-gated ion channel; ω-conotoxins and the voltage-gated calcium channel; μ-conotoxins and the voltage-gated sodium channel; δ-conotoxins and the voltage-gated sodium channel; κ-conotoxins and the voltage-gated potassium channel; conantokins and the ligand-gated glutamate (NMDA) channel.

[0007] However, the structure and function of only a small minority of these peptides have been determined to date. For peptides where function has been determined, three classes of targets have been elucidated: voltage-gated ion channels; ligand-gated ion channels, and G-protein-linked receptors.

[0008] *Conus* peptides which target voltage-gated ion channels include those that delay the inactivation of sodium channels, as well as blockers specific for sodium channels, calcium channels and potassium channels. Peptides that target ligand-gated ion channels include antagonists of NMDA and serotonin receptors, as well as competitive and noncompetitive nicotinic receptor antagonists. Peptides which act on G-protein receptors include neurotensin and vasopressin receptor agonists. The unprecedented pharmaceutical selectivity of conotoxins is at least in part defined by a specific disulfide bond frameworks combined with hypervariable amino acids within disulfide loops (for a review see McIntosh et al., 1998).

[0009] There are drugs used in the treatment of pain, which are known in the literature and to the skilled artisan. See, for example, Merck Manual, 16th Ed. (1992). However, there is a demand for more active analgesic agents with diminished side effects and toxicity and which are non-addictive. The ideal analgesic would reduce the awareness of pain, produce analgesia over a

wide range of pain types, act satisfactorily whether given orally or parenterally, produce minimal or no side effects, be free from tendency to produce tolerance and drug dependence.

[0010] Due to the high potency and exquisite selectivity of the conopeptides, several are in various stages of clinical development for treatment of human disorders. For example, two *Conus* peptides are being developed for the treatment of pain. The most advanced is ω-conotoxin MVIIA (ziconotide), an N-type calcium channel blocker (see Heading, C., 1999; U.S. Patent No. 5,859,186). ω-Conotoxin MVIIA, isolated from *Conus magus*, is approximately 1000 times more potent than morphine, yet does not produce the tolerance or addictive properties of opiates. ω-Conotoxin MVIIA has completed Phase III (final stages) of human clinical trials and has been approved as a therapeutic agent. ω-Conotoxin MVIIA is introduced into human patients by means of an implantable, programmable pump with a catheter threaded into the intrathecal space. Preclinical testing for use in post-surgical pain is being carried out on another *Conus* peptide, contulakin-G, isolated from *Conus geographus* (Craig et al. 1999). Contulakin-G is a 16 amino acid O-linked glycopeptide whose C-terminus resembles neurotensin. It is an agonist of neurotensin receptors, but appears significantly more potent than neurotensin in inhibiting pain in *in vivo* assays.

[0011] Ischemic damage to the central nervous system (CNS) may result form either global or focal ischemic conditions. Global ischemia occurs under conditions in which blood flow to the entire brain ceases for a period of time, such as may result from cardiac arrest. Focal ischemia occurs under conditions in which a portion of the brain is deprived of its normal blood supply, such as may result from thromboembolytic occlusion of a cerebral vessel, traumatic head or spinal cord injury, edema or brain or spinal cord tumors. Both global and focal ischemic conditions have the potential for widespread neuronal damage, even if the global ischemic condition is transient or the focal condition affects a very limited area.

[0012] Epilepsy is a recurrent paroxysmal disorder of cerebral function characterized by sudden brief attacks of altered consciousness, motor activity, sensory phenomena or inappropriate behavior caused by abnormal excessive discharge of cerebral neurons. Convulsive seizures, the most common form of attacks, begin with loss of consciousness and motor control, and tonic or clonic jerking of all extremities but any recurrent seizure pattern may be termed epilepsy. The term primary or idiopathic epilepsy denotes those cases where no cause for the seizures can be identified. Secondary or symptomatic epilepsy designates the disorder when it is associated with such factors as trauma, neoplasm, infection, developmental abnormalities,

cerebrovascular disease, or various metabolic conditions. Epileptic seizures are classified as partial seizures (focal, local seizures) or generalized seizures (convulsive or nonconvulsive). Classes of partial seizures include simple partial seizures, complex partial seizures and partial seizures secondarily generalized. Classes of generalized seizures include absence seizures, atypical absence seizures, myoclonic seizures, clonic seizures, tonic seizures, tonic-clonic seizures (*grand mal*) and atonic seizures. Therapeutics having anticonvulsant properties are used in the treatment of seizures. Most therapeutics used to abolish or attenuate seizures act at least through effects that reduce the spread of excitation from seizure foci and prevent detonation and disruption of function of normal aggregates of neurons. Traditional anticonvulsants that have been utilized include phenytoin, phenobarbital, primidone, carbamazepine, ethosuximide, clonazepam and valproate. Several novel and chemically diverse anticonvulsant medications recently have been approved for marketing, including lamotrigine, ferlbamate, gabapentin and topiramate. For further details of seizures and their therapy, see Rall & Schleifer (1985) and *The Merck Manual* (1992).

[0013] In view of a large number of biologically active substances in *Conus* species it is desirable to further characterize them and to identify peptides capable of treating disorders involving voltage gated ion channels, such as stroke and pain. Surprisingly, and in accordance with this invention, Applicants have discovered novel conotoxins that can be useful for the treatment of disorders involving voltage gated ion channels and could address a long felt need for a safe and effective treatment.

SUMMARY OF THE INVENTION

[0014] The present invention is directed to ω-conopeptides, derivatives or pharmaceutically acceptable salts thereof, and uses thereof, including the treatment of neurologic and psychiatric disorders, such as anticonvulsant agents, as neuroprotective agents, as cardiovascular agents or for the management of pain. The invention is further directed to nucleic acid sequences encoding the ω-conopeptides and encoding propeptides, as well as the propeptides.

[0015] More specifically, the present invention is directed to ω-conopeptides, having the amino acid sequences set forth in Table 2 below.

[0016] The present invention is also directed to derivatives or pharmaceutically acceptable salts of the ω-conopeptides or the derivatives. Examples of derivatives include

peptides in which the Arg residues may be substituted by Lys, ornithine, homoargine, nor-Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any synthetic basic amino acid; the Lys residues may be substituted by Arg, ornithine, homoargine, nor-Lys, or any synthetic basic amino acid; the Tyr residues may be substituted with meta-Tyr, ortho-Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any synthetic hydroxy containing amino acid; the Ser residues may be substituted with Thr or any synthetic hydroxylated amino acid; the Thr residues may be substituted with Ser or any synthetic hydroxylated amino acid; the Phe residues may be substituted with any synthetic aromatic amino acid; the Trp residues may be substituted with Trp (D), neo-Trp, halo-Trp (D or L) or any aromatic synthetic amino acid; and the Asn, Ser, Thr or Hyp residues may be glycosylated. The halogen may be iodo, chloro, fluoro or bromo; preferably iodo for halogen substituted-Tyr and bromo for halogen-substituted Trp. The Tyr residues may also be substituted with the 3-hydroxyl or 2-hydroxyl isomers (meta-Tyr or ortho-Tyr, respectively) and corresponding O-sulpho- and O-phospho-derivatives. The acidic amino acid residues may be substituted with any synthetic acidic amino acid, e.g., tetrazolyl derivatives of Gly and Ala. The aliphatic amino acids may be substituted by synthetic derivatives bearing non-natural aliphatic branched or linear side chains C_nH_{2n+2} up to and including n=8. The Cys residues may be in D or L configuration and may optionally be substituted with homocysteine (D or L).

[0017] Examples of synthetic aromatic amino acid include, but are not limited to, nitro-Phe, 4-substituted-Phe wherein the substituent is C_1-C_3 alkyl, carboxyl, hydroxymethyl, sulphomethyl, halo, phenyl, -CHO, -CN, -SO_3H and -NHAc. Examples of synthetic hydroxy containing amino acid, include, but are not limited to, such as 4-hydroxymethyl-Phe, 4-hydroxyphenyl-Gly, 2,6-dimethyl-Tyr and 5-amino-Tyr. Examples of synthetic basic amino acids include, but are not limited to, N-1-(2-pyrazolinyl)-Arg, 2-(4-piperinyl)-Gly, 2-(4-piperinyl)-Ala, 2-[3-(2S)pyrrolininyl)-Gly and 2-[3-(2S)pyrrolininyl)-Ala. These and other synthetic basic amino acids, synthetic hydroxy containing amino acids or synthetic aromatic amino acids are described in Building Block Index, Version 3.0 (1999 Catalog, pages 4-47 for hydroxy containing amino acids and aromatic amino acids and pages 66-87 for basic amino acids; see also http://www.amino-acids.com), incorporated herein by reference, by and available from RSP Amino Acid Analogues, Inc., Worcester, MA. Examples of synthetic acid amino acids include those derivatives bearing acidic functionality, including carboxyl, phosphate,

sulfonate and synthetic tetrazolyl derivatives such as described by Ornstein et al. (1993) and in U.S. Patent No. 5,331,001, each incorporated herein by reference.

[0018] Optionally, in the ω-conopeptides of the present invention, the Asn residues may be modified to contain an N-glycan and the Ser, Thr and Hyp residues may be modified to contain an O-glycan (e.g., g-N, g-S, g-T and g-Hyp). In accordance with the present invention, a glycan shall mean any N-, S- or O-linked mono-, di-, tri-, poly- or oligosaccharide that can be attached to any hydroxy, amino or thiol group of natural or modified amino acids by synthetic or enzymatic methodologies known in the art. The monosaccharides making up the glycan can include D-allose, D-altrose, D-glucose, D-mannose, D-gulose, D-idose, D-galactose, D-talose, D-galactosamine, D-glucosamine, D-N-acetyl-glucosamine (GlcNAc), D-N-acetyl-galactosamine (GalNAc), D-fucose or D-arabinose. These saccharides may be structurally modified, e.g., with one or more O-sulfate, O-phosphate, O-acetyl or acidic groups, such as sialic acid, including combinations thereof. The glycan may also include similar polyhydroxy groups, such as D-penicillamine 2,5 and halogenated derivatives thereof or polypropylene glycol derivatives. The glycosidic linkage is beta and 1-4 or 1-3, preferably 1-3. The linkage between the glycan and the amino acid may be alpha or beta, preferably alpha and is 1-.

[0019] Core O-glycans have been described by Van de Steen et al. (1998), incorporated herein by reference. Mucin type O-linked oligosaccharides are attached to Ser or Thr (or other hydroxylated residues of the present peptides) by a GalNAc residue. The monosaccharide building blocks and the linkage attached to this first GalNAc residue define the "core glycans," of which eight have been identified. The type of glycosidic linkage (orientation and connectivities) are defined for each core glycan. Suitable glycans and glycan analogs are described further in U.S. Serial No. 09/420,797 filed 19 October 1999 and in PCT Application No. PCT/US99/24380 filed 19 October 1999 (PCT Published Application No. WO 00/23092), each incorporated herein by reference. A preferred glycan is Gal(β1→3)GalNAc(α1→).

[0020] Optionally, in the ω-conopeptides described above, pairs of Cys residues may be replaced pairwise with isoteric lactam or ester-thioether replacements, such as Ser/(Glu or Asp), Lys/(Glu or Asp) or Cys/Ala combinations. Sequential coupling by known methods (Barnay et al., 2000; Hruby et al., 1994; Bitan et al., 1997) allows replacement of native Cys bridges with lactam bridges. Thioether analogs may be readily synthesized using halo-Ala residues commercially available from RSP Amino Acid Analogues.

[0021] The present invention is further directed to a method of treating disorders associated with voltage gated ion channel disorders in a subject comprising administering to the subject an effective amount of the pharmaceutical composition comprising a therapeutically effective amount of a ω-conopeptide described herein or a pharmaceutically acceptable salt or solvate thereof. The present invention is also directed to a pharmaceutical composition comprising a therapeutically effective amount of a ω-conopeptide described herein or a pharmaceutically acceptable salt or solvate thereof and a pharmaceutically acceptable carrier.

[0022] More specifically, the present invention is further directed to uses of these peptides or nucleic acids as described herein, including the treatment of neurologic disorders, such as anticonvulsant agents, as neuroprotective agents, such as for treating stroke, as cardiovascular agents or for the management of pain.

[0023] More specifically, the present invention is also directed to nucleic acids which encode conopeptides of the present invention or which encodes precursor peptides for these conopeptides, as well as the precursor peptide. The nucleic acid sequences encoding the precursor peptides of other conopeptides of the present invention are set forth in Table 1. Table 1 also sets forth the amino acid sequences of these precursor peptides.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0024] The present invention is to ω-conopeptides, derivatives or pharmaceutically acceptable salts thereof. The present invention is further directed to the use of this peptide, derivatives thereof and pharmaceutically acceptable salts thereof for the treatment of neurologic disorders, such as anticonvulsant agents, as neuroprotective agents, such as for treating stroke, as cardiovascular agents or for the management of pain, e.g. as analgesic agents. The invention is further directed to nucleic acid sequences encoding the ω-conopeptides and encoding propeptides, as well as the propeptides.

[0025] The present invention, in another aspect, relates to a pharmaceutical composition comprising an effective amount of an ω-conopeptides, a mutein thereof, an analog thereof, an active fragment thereof or pharmaceutically acceptable salts or solvates. Such a pharmaceutical composition has the capability of acting at voltage gated ion channels, and are thus useful for treating a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to the partial or complete blockade of voltage gated ion channels of the central nervous system comprising the step of administering to such a living animal body,

including a human, in need thereof a therapeutically effective amount of a pharmaceutical composition of the present invention.

[0026] Voltage-gated calcium channels are present in neurons, and in cardiac, smooth, and skeletal muscle and other excitable cells, and are known to play a variety of roles in membrane excitability, muscle contraction, and cellular secretion, such as in synaptic transmission (McCleskey). In neuronal cells, voltage-gated calcium channels have been classified by their electrophysiological as well as by their biochemical (binding) properties. Six classes of physiologically distinct calcium channels have been identified to date, namely the T, L, N, P, Q, and R-type channels.

[0027] It is well known that an accumulation of calcium (calcium overload) in the brain is seen after anoxia, ischemia, migraine and other hyperactivity periods of the brain, such as after epileptic convulsions. An uncontrolled high concentration of calcium in the cells of the central nervous system (CNS) is known to cause most of the degenerative changes connected with the above diseases. Compounds which can block the calcium channels of brain cells are therefore useful in the treatment of stroke, anoxia, ischemia, migraine, psychosis, or epilepsy, any other convulsive disorder and in the prevention of the degenerative changes connected with the same.

[0028] Compounds blocking the so called L-type calcium channels in the CNS are useful for the treatment of the above disorders by directly blocking the calcium uptake in the CNS. Further, it is well known that the so called N- and P-types of calcium channels, as well as possibly other types of calcium channels, are involved in the regulation of neurotransmitter release. Compounds blocking the N- and/or P-types of calcium channels indirectly and very powerfully prevent calcium overload in the CNS after the hyperactivity periods of the brain as described above by inhibiting the enhanced neurotransmitter release seen after such hyperactivity periods of the CNS, and especially the neurotoxic, enhanced glutamate release after such hyperactivity periods of the CNS. Furthermore, blockers of the N- and/or P-types of calcium channels, as dependent upon the selectivity of the compound in question, inhibit the release of various other neurotransmitters such as aspartate, GABA, glycine, dopamine, serotonin and noradrenaline.

[0029] Thus, the pharmaceutical compositions of the present invention are useful as neuroprotectants, cardiovascular agents, anticonvulsants, analgesics or adjuvants to general anesthetics. A "neurological disorder or disease" is a disorder or disease of the nervous system including, but not limited to, global and focal ischemic and hemorrhagic stroke, head trauma,

spinal cord injury, hypoxia-induced nerve cell damage as in cardiac arrest or neonatal distress or epilepsy. In addition, a "neurological disorder or disease" is a disease state and condition in which a neuroprotectant, anticonvulsant, analgesic and/or as an adjunct in general anesthesia may be indicated, useful, recommended or prescribed.

[0030] More specifically, the present invention is directed to the use of these compounds for the treatment and alleviation of epilepsy and as a general anticonvulsant agent. The present invention is also directed to the use of these compounds for reducing neurotoxic injury associated with conditions of hypoxia, anoxia or ischemia which typically follows stroke, cerebrovascular accident, brain or spinal cord trauma, myocardial infarct, physical trauma, drowning, suffocation, perinatal asphyxia, or hypoglycemic events. The present invention is further directed to the use of these compounds for treating pain, including acute and chronic pain, such migraine, nociceptive and neuropathic pain. Other uses of these compounds are described in U.S. Patent No. 5,859,186, incorporated herein by reference.

[0031] A "neuroprotectant" is a compound capable of preventing the neuronal death associated with a neurological disorder or disease. An "anticonvulsant" is a compound capable of reducing convulsions produced by conditions such as simple partial seizures, complex partial seizures, status epilepticus, and trauma-induced seizures such as occur following head injury, including head surgery. An "analgesic" is a compound capable of relieving pain by altering perception of nociceptive stimuli without producing anesthesia or loss of consciousness. A "muscle relaxant" is a compound that reduces muscular tension. A "adjunct in general anesthesia" is a compound useful in conjunction with anesthetic agents in producing the loss of ability to perceive pain associated with the loss of consciousness.

[0032] The invention relates as well to methods useful for treatment of neurological disorders and diseases, including, but not limited to, global and focal ischemic and hemorrhagic stroke, head trauma, spinal cord injury, hypoxia-induced nerve cell damage such as in cardiac arrest or neonatal distress, epilepsy or other convulsive disorders without undesirable side effects.

[0033] Thus, in one embodiment, the invention provides a method of reducing/alleviating/ decreasing the perception of pain by a subject or for inducing analgesia in a subject comprising administering to the subject an effective amount of the pharmaceutical composition comprising a therapeutically effective amount of a ω-conopeptide described herein

or a pharmaceutically acceptable salt or solvate thereof. The pain may be acute, persistent, inflammatory or neuropathic pain.

[0034] In a second embodiment, the invention provides a method of treating stroke, head or spinal cord trauma or injury, anoxia, hypoxia-induced nerve cell damage, ischemia, migraine, psychosis, anxiety, schizophrenia, inflammation, movement disorder, epilepsy, any other convulsive disorder or in the prevention of the degenerative changes connected with the same in a subject comprising administering to the subject an effective amount of the pharmaceutical composition comprising a therapeutically effective amount of a ω-conopeptide described herein or a pharmaceutically acceptable salt or solvate thereof.

[0035] The ω-conopeptides described herein are sufficiently small to be chemically synthesized. General chemical syntheses for preparing the foregoing ω-conotoxin peptides are described hereinafter. Various ones of the ω-conopeptides can also be obtained by isolation and purification from specific *Conus* species using the technique described in U.S. Patent Nos. 4,447,356 (Olivera et al., 1984); 5,514,774; 5,719,264; and 5,591,821, as well as in PCT published application WO 98/03189, the disclosures of which are incorporated herein by reference.

[0036] Although the ω-conopeptides of the present invention can be obtained by purification from cone snails, because the amounts of ω-conopeptides obtainable from individual snails are very small, the desired substantially pure ω-conopeptides are best practically obtained in commercially valuable amounts by chemical synthesis using solid-phase strategy. For example, the yield from a single cone snail may be about 10 micrograms or less of ω-conopeptides peptide. By "substantially pure" is meant that the peptide is present in the substantial absence of other biological molecules of the same type; it is preferably present in an amount of at least about 85% purity and preferably at least about 95% purity. Chemical synthesis of biologically active ω-conopeptides peptides depends of course upon correct determination of the amino acid sequence.

[0037] The ω-conopeptides can also be produced by recombinant DNA techniques well known in the art. Such techniques are described by Sambrook et al. (1989). A gene of interest (i.e., a gene that encodes a suitable ω-conopeptides) can be inserted into a cloning site of a suitable expression vector by using standard techniques. These techniques are well known to those skilled in the art. The expression vector containing the gene of interest may then be used to transfect the desired cell line. Standard transfection techniques such as calcium phosphate

co-precipitation, DEAE-dextran transfection or electroporation may be utilized. A wide variety of host/expression vector combinations may be used to express a gene encoding a conotoxin peptide of interest. Such combinations are well known to a skilled artisan. The peptides produced in this manner are isolated, reduced if necessary, and oxidized to form the correct disulfide bonds.

[0038] One method of forming disulfide bonds in the ω-conopeptides of the present invention is the air oxidation of the linear peptides for prolonged periods under cold room temperatures or at room temperature. This procedure results in the creation of a substantial amount of the bioactive, disulfide-linked peptides. The oxidized peptides are fractionated using reverse-phase high performance liquid chromatography (HPLC) or the like, to separate peptides having different linked configurations. Thereafter, either by comparing these fractions with the elution of the native material or by using a simple assay, the particular fraction having the correct linkage for maximum biological potency is easily determined. However, because of the dilution resulting from the presence of other fractions of less biopotency, a somewhat higher dosage may be required.

[0039] The peptides are synthesized by a suitable method, such as by exclusively solid-phase techniques, by partial solid-phase techniques, by fragment condensation or by classical solution couplings.

[0040] In conventional solution phase peptide synthesis, the peptide chain can be prepared by a series of coupling reactions in which constituent amino acids are added to the growing peptide chain in the desired sequence. Use of various coupling reagents, e.g., dicyclohexylcarbodiimide or diisopropylcarbonyldimidazole, various active esters, e.g., esters of N-hydroxyphthalimide or N-hydroxy-succinimide, and the various cleavage reagents, to carry out reaction in solution, with subsequent isolation and purification of intermediates, is well known classical peptide methodology. Classical solution synthesis is described in detail in the treatise, "Methoden der Organischen Chemie (Houben-Weyl): Synthese von Peptiden," (1974). Techniques of exclusively solid-phase synthesis are set forth in the textbook, "Solid-Phase Peptide Synthesis," (Stewart and Young, 1969), and are exemplified by the disclosure of U.S. Patent 4,105,603 (Vale et al., 1978). The fragment condensation method of synthesis is exemplified in U.S. Patent 3,972,859 (1976). Other available syntheses are exemplified by U.S. Patents No. 3,842,067 (1974) and 3,862,925 (1975). The synthesis of peptides containing γ-

carboxyglutamic acid residues is exemplified by Rivier et al. (1987), Nishiuchi et al. (1993) and Zhou et al. (1996).

[0041] Common to such chemical syntheses is the protection of the labile side chain groups of the various amino acid moieties with suitable protecting groups which will prevent a chemical reaction from occurring at that site until the group is ultimately removed. Usually also common is the protection of an α-amino group on an amino acid or a fragment while that entity reacts at the carboxyl group, followed by the selective removal of the α-amino protecting group to allow subsequent reaction to take place at that location. Accordingly, it is common that, as a step in such a synthesis, an intermediate compound is produced which includes each of the amino acid residues located in its desired sequence in the peptide chain with appropriate side-chain protecting groups linked to various ones of the residues having labile side chains.

[0042] As far as the selection of a side chain amino protecting group is concerned, generally one is chosen which is not removed during deprotection of the α-amino groups during the synthesis. However, for some amino acids, e.g., His, protection is not generally necessary. In selecting a particular side chain protecting group to be used in the synthesis of the peptides, the following general rules are followed: (a) the protecting group preferably retains its protecting properties and is not split off under coupling conditions, (b) the protecting group should be stable under the reaction conditions selected for removing the α-amino protecting group at each step of the synthesis, and (c) the side chain protecting group must be removable, upon the completion of the synthesis containing the desired amino acid sequence, under reaction conditions that will not undesirably alter the peptide chain.

[0043] It should be possible to prepare many, or even all, of these peptides using recombinant DNA technology. However, when peptides are not so prepared, they are preferably prepared using the Merrifield solid-phase synthesis, although other equivalent chemical syntheses known in the art can also be used as previously mentioned. Solid-phase synthesis is commenced from the C-terminus of the peptide by coupling a protected α-amino acid to a suitable resin. Such a starting material can be prepared by attaching an α-amino-protected amino acid by an ester linkage to a chloromethylated resin or a hydroxymethyl resin, or by an amide bond to a benzhydrylamine (BHA) resin or paramethylbenzhydrylamine (MBHA) resin. Preparation of the hydroxymethyl resin is described by Bodansky et al. (1966). Chloromethylated resins are commercially available from Bio Rad Laboratories (Richmond, CA) and from Lab. Systems, Inc. The preparation of such a resin is described by Stewart and

Young (1969). BHA and MBHA resin supports are commercially available, and are generally used when the desired polypeptide being synthesized has an unsubstituted amide at the C-terminus. Thus, solid resin supports may be any of those known in the art, such as one having the formulae -O-CH_2-resin support, -NH BHA resin support, or -NH-MBHA resin support. When the unsubstituted amide is desired, use of a BHA or MBHA resin is preferred, because cleavage directly gives the amide. In case the N-methyl amide is desired, it can be generated from an N-methyl BHA resin. Should other substituted amides be desired, the teaching of U.S. Patent No. 4,569,967 (Kornreich et al., 1986) can be used, or should still other groups than the free acid be desired at the C-terminus, it may be preferable to synthesize the peptide using classical methods as set forth in the Houben-Weyl text (1974).

[0044] The C-terminal amino acid, protected by Boc or Fmoc and by a side-chain protecting group, if appropriate, can be first coupled to a chloromethylated resin according to the procedure set forth in K. Horiki et al. (1978), using KF in DMF at about 60°C for 24 hours with stirring, when a peptide having free acid at the C-terminus is to be synthesized. Following the coupling of the BOC-protected amino acid to the resin support, the α-amino protecting group is removed, as by using trifluoroacetic acid (TFA) in methylene chloride or TFA alone. The deprotection is carried out at a temperature between about 0°C and room temperature. Other standard cleaving reagents, such as HCl in dioxane, and conditions for removal of specific α-amino protecting groups may be used as described in Schroder & Lubke (1965).

[0045] After removal of the α-amino-protecting group, the remaining α-amino- and side chain-protected amino acids are coupled step-wise in the desired order to obtain the intermediate compound defined hereinbefore, or as an alternative to adding each amino acid separately in the synthesis, some of them may be coupled to one another prior to addition to the solid phase reactor. Selection of an appropriate coupling reagent is within the skill of the art. Particularly suitable as a coupling reagent is N,N'-dicyclohexylcarbodiimide (DCC, DIC, HBTU, HATU, TBTU in the presence of HoBt or HoAt).

[0046] The activating reagents used in the solid phase synthesis of the peptides are well known in the peptide art. Examples of suitable activating reagents are carbodiimides, such as N,N'-diisopropylcarbodiimide and N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide. Other activating reagents and their use in peptide coupling are described by Schroder & Lubke (1965) and Kapoor (1970).

[0047] Each protected amino acid or amino acid sequence is introduced into the solid-phase reactor in about a twofold or more excess, and the coupling may be carried out in a medium of dimethylformamide (DMF):CH_2Cl_2 (1:1) or in DMF or CH_2Cl_2 alone. In cases where intermediate coupling occurs, the coupling procedure is repeated before removal of the α-amino protecting group prior to the coupling of the next amino acid. The success of the coupling reaction at each stage of the synthesis, if performed manually, is preferably monitored by the ninhydrin reaction, as described by Kaiser et al. (1970). Coupling reactions can be performed automatically, as on a Beckman 990 automatic synthesizer, using a program such as that reported in Rivier et al. (1978).

[0048] After the desired amino acid sequence has been completed, the intermediate peptide can be removed from the resin support by treatment with a reagent, such as liquid hydrogen fluoride or TFA (if using Fmoc chemistry), which not only cleaves the peptide from the resin but also cleaves all remaining side chain protecting groups and also the -amino protecting group at the N-terminus if it was not previously removed to obtain the peptide in the form of the free acid. If Met is present in the sequence, the Boc protecting group is preferably first removed using trifluoroacetic acid (TFA)/ethanedithiol prior to cleaving the peptide from the resin with HF to eliminate potential S-alkylation. When using hydrogen fluoride or TFA for cleaving, one or more scavengers such as anisole, cresol, dimethyl sulfide and methylethyl sulfide are included in the reaction vessel.

[0049] Cyclization of the linear peptide is preferably affected, as opposed to cyclizing the peptide while a part of the peptido-resin, to create bonds between Cys residues. To effect such a disulfide cyclizing linkage, fully protected peptide can be cleaved from a hydroxymethylated resin or a chloromethylated resin support by ammonolysis, as is well known in the art, to yield the fully protected amide intermediate, which is thereafter suitably cyclized and deprotected. Alternatively, deprotection, as well as cleavage of the peptide from the above resins or a benzhydrylamine (BHA) resin or a methylbenzhydrylamine (MBHA), can take place at 0°C with hydrofluoric acid (HF) or TFA, followed by oxidation as described above.

[0050] The peptides are also synthesized using an automatic synthesizer. Amino acids are sequentially coupled to an MBHA Rink resin (typically 100 mg of resin) beginning at the C-terminus using an Advanced Chemtech 357 Automatic Peptide Synthesizer. Couplings are carried out using 1,3-diisopropylcarbodimide in N-methylpyrrolidinone (NMP) or by 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and diethylisopro-

pylethylamine (DIEA). The FMOC protecting group is removed by treatment with a 20% solution of piperidine in dimethylformamide(DMF). Resins are subsequently washed with DMF (twice), followed by methanol and NMP.

[0051] Muteins, analogs or active fragments, of the foregoing conotoxin peptides are also contemplated here. See, e.g., Hammerland et al. (1992). Derivative muteins, analogs or active fragments of the conotoxin peptides may be synthesized according to known techniques, including conservative amino acid substitutions, such as outlined in U.S. Patent Nos. 5,545,723 (see particularly col. 2, line 50--col. 3, line 8); 5,534,615 (see particularly col. 19, line 45--col. 22, line 33); and 5,364,769 (see particularly col. 4, line 55--col. 7, line 26), each herein incorporated by reference.

[0052] The ω-conopeptides of the present invention are also useful to reduce neurotoxic injury associated with conditions of hypoxia, anoxia or ischemia which typically follows stroke, cerebrovascular accident, brain or spinal chord trauma, myocardial infarct, physical trauma, drownings, suffocation, perinatal asphyxia, or hypoglycemic events. To reduce neurotoxic injury, an ω-conopeptide should be administered in a therapeutically effective amount to the patient within 24 hours of the onset of the hypoxic, anoxic or ischemic condition in order for the ω-conopeptide to effectively minimize the CNS damage which the patient will experience.

[0053] The ω-conopeptides of the present invention are further useful in controlling pain, e.g., as analgesic agents, and the treatment of migraine, acute pain or persistent pain. They can be used prophylactically or to relieve the symptoms associated with a migraine episode, or to treat acute or persistent pain. For these uses, an ω-conopeptide is administered in a therapeutically effective amount to overcome or to ease the pain.

[0054] Pharmaceutical compositions containing a compound of the present invention as the active ingredient can be prepared according to conventional pharmaceutical compounding techniques. See, for example, *Remington's Pharmaceutical Sciences*, 18th Ed. (1990, Mack Publishing Co., Easton, PA). Typically, an antagonistic amount of active ingredient will be admixed with a pharmaceutically acceptable carrier. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., intravenous, oral, parenteral or intrathecally. For examples of delivery methods see U.S. Patent No. 5,844,077, incorporated herein by reference.

[0055] "Pharmaceutical composition" means physically discrete coherent portions suitable for medical administration. "Pharmaceutical composition in dosage unit form" means

physically discrete coherent units suitable for medical administration, each containing a daily dose or a multiple (up to four times) or a sub-multiple (down to a fortieth) of a daily dose of the active compound in association with a carrier and/or enclosed within an envelope. Whether the composition contains a daily dose, or for example, a half, a third or a quarter of a daily dose, will depend on whether the pharmaceutical composition is to be administered once or, for example, twice, three times or four times a day, respectively.

[0056] The term "salt", as used herein, denotes acidic and/or basic salts, formed with inorganic or organic acids and/or bases, preferably basic salts. While pharmaceutically acceptable salts are preferred, particularly when employing the compounds of the invention as medicaments, other salts find utility, for example, in processing these compounds, or where non-medicament-type uses are contemplated. Salts of these compounds may be prepared by art-recognized techniques.

[0057] Examples of such pharmaceutically acceptable salts include, but are not limited to, inorganic and organic addition salts, such as hydrochloride, sulphates, nitrates or phosphates and acetates, trifluoroacetates, propionates, succinates, benzoates, citrates, tartrates, fumarates, maleates, methane-sulfonates, isothionates, theophylline acetates, salicylates, respectively, or the like. Lower alkyl quaternary ammonium salts and the like are suitable, as well.

[0058] As used herein, the term "pharmaceutically acceptable" carrier means a non-toxic, inert solid, semi-solid liquid filler, diluent, encapsulating material, formulation auxiliary of any type, or simply a sterile aqueous medium, such as saline. Some examples of the materials that can serve as pharmaceutically acceptable carriers are sugars, such as lactose, glucose and sucrose, starches such as corn starch and potato starch, cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt, gelatin, talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol, polyols such as glycerin, sorbitol, mannitol and polyethylene glycol; esters such as ethyl oleate and ethyl laurate, agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline, Ringer's solution; ethyl alcohol and phosphate buffer solutions, as well as other non-toxic compatible substances used in pharmaceutical formulations.

[0059] Wetting agents, emulsifiers and lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening,

flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator. Examples of pharmaceutically acceptable antioxidants include, but are not limited to, water soluble antioxidants such as ascorbic acid, cysteine hydrochloride, sodium bisulfite, sodium metabisulfite, sodium sulfite, and the like; oil soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, aloha-tocopherol and the like; and the metal chelating agents such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid and the like.

[0060] For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, lozenges, melts, powders, suspensions or emulsions.

In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, suspending agents, and the like in the case of oral liquid preparations (such as, for example, suspensions, elixirs and solutions); or carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations (such as, for example, powders, capsules and tablets). Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar-coated or enteric-coated by standard techniques. The active agent can be encapsulated to make it stable to passage through the gastrointestinal tract while at the same time allowing for passage across the blood brain barrier. See for example, WO 96/11698.

[0061] For parenteral administration, the compound may be dissolved in a pharmaceutical carrier and administered as either a solution or a suspension. Illustrative of suitable carriers are water, saline, dextrose solutions, fructose solutions, ethanol, or oils of animal, vegetative or synthetic origin. The carrier may also contain other ingredients, for example, preservatives, suspending agents, solubilizing agents, buffers and the like. When the compounds are being administered intrathecally, they may also be dissolved in cerebrospinal fluid.

[0062] A variety of administration routes are available. The particular mode selected will depend of course, upon the particular drug selected, the severity of the disease state being treated and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable,

meaning any mode that produces effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, sublingual, topical, nasal, transdermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, epidural, irrigation, intramuscular, release pumps, or infusion.

[0063] For example, administration of the active agent according to this invention may be achieved using any suitable delivery means, including:

(a) pump (see, e.g., Luer & Hatton (1993), Zimm et al. (1984) and Ettinger et al. (1978));

(b) microencapsulation (see, e.g., U.S. Patent Nos. 4,352,883; 4,353,888; and 5,084,350);

(c) continuous release polymer implants (see, e.g., U.S. Patent No. 4,883,666);

(d) macroencapsulation (see, e.g., U.S. Patent Nos. 5,284,761, 5,158,881, 4,976,859 and 4,968,733 and published PCT patent applications WO92/19195, WO 95/05452);

(e) naked or unencapsulated cell grafts to the CNS (see, e.g., U.S. Patent Nos. 5,082,670 and 5,618,531);

(f) injection, either subcutaneously, intravenously, intra-arterially, intramuscularly, or to other suitable site; or

(g) oral administration, in capsule, liquid, tablet, pill, or prolonged release formulation.

[0064] In one embodiment of this invention, an active agent is delivered directly into the CNS, preferably to the brain ventricles, brain parenchyma, the intrathecal space or other suitable CNS location, most preferably intrathecally.

[0065] Alternatively, targeting therapies may be used to deliver the active agent more specifically to certain types of cell, by the use of targeting systems such as antibodies or cell specific ligands. Targeting may be desirable for a variety of reasons, e.g. if the agent is unacceptably toxic, or if it would otherwise require too high a dosage, or if it would not otherwise be able to enter the target cells.

[0066] The active agents, which are peptides, can also be administered in a cell based delivery system in which a DNA sequence encoding an active agent is introduced into cells designed for implantation in the body of the patient, especially in the spinal cord region. Suitable delivery systems are described in U.S. Patent No. 5,550,050 and published PCT Application Nos. WO 92/19195, WO 94/25503, WO 95/01203, WO 95/05452, WO 96/02286, WO 96/02646, WO 96/40871, WO 96/40959 and WO 97/12635. Suitable DNA sequences can

be prepared synthetically for each active agent on the basis of the developed sequences and the known genetic code.

[0067] The active agent is preferably administered in an therapeutically effective amount. By a "therapeutically effective amount" or simply "effective amount" of an active compound is meant a sufficient amount of the compound to treat the desired condition at a reasonable benefit/risk ratio applicable to any medical treatment. The actual amount administered, and the rate and time-course of administration, will depend on the nature and severity of the condition being treated. Prescription of treatment, e.g. decisions on dosage, timing, etc., is within the responsibility of general practitioners or specialists, and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners. Examples of techniques and protocols can be found in *Remington's Pharmaceutical Sciences*.

[0068] Dosage may be adjusted appropriately to achieve desired drug levels, locally or systemically. Typically the active agents of the present invention exhibit their effect at a dosage range from about 0.001 mg/kg to about 250 mg/kg, preferably from about 0.01 mg/kg to about 100 mg/kg of the active ingredient, more preferably from a bout 0.05 mg/kg to about 75 mg/kg. A suitable dose can be administered in multiple sub-doses per day. Typically, a dose or sub-dose may contain from about 0.1 mg to about 500 mg of the active ingredient per unit dosage form. A more preferred dosage will contain from about 0.5 mg to about 100 mg of active ingredient per unit dosage form. Dosages are generally initiated at lower levels and increased until desired effects are achieved. In the event that the response in a subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Continuous dosing over, for example 24 hours or multiple doses per day are contemplated to achieve appropriate systemic levels of compounds.

[0069] For the treatment of pain, if the route of administration is directly to the CNS, the dosage contemplated is from about 1 ng to about 100 mg per day, preferably from about 100 ng to about 10 mg per day, more preferably from about 1 μg to about 100 μg per day. If administered peripherally, the dosage contemplated is somewhat higher, from about 100 ng to about 1000 mg per day, preferably from about 10 μg to about 100 mg per day, more preferably from about 100 μg to about 10 mg per day. If the conopeptide is delivered by continuous

infusion (e.g., by pump delivery, biodegradable polymer delivery or cell-based delivery), then a lower dosage is contemplated than for bolus delivery.

[0070] Advantageously, the compositions are formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredients. Tablets, coated tablets, capsules, ampoules and suppositories are examples of dosage forms according to the invention.

[0071] It is only necessary that the active ingredient constitute an effective amount, i.e., such that a suitable effective dosage will be consistent with the dosage form employed in single or multiple unit doses. The exact individual dosages, as well as daily dosages, are determined according to standard medical principles under the direction of a physician or veterinarian for use humans or animals.

[0072] The pharmaceutical compositions will generally contain from about 0.0001 to 99 wt. %, preferably about 0.001 to 50 wt. %, more preferably about 0.01 to 10 wt.% of the active ingredient by weight of the total composition. In addition to the active agent, the pharmaceutical compositions and medicaments can also contain other pharmaceutically active compounds. Examples of other pharmaceutically active compounds include, but are not limited to, analgesic agents, cytokines and therapeutic agents in all of the major areas of clinical medicine. When used with other pharmaceutically active compounds, the conopeptides of the present invention may be delivered in the form of drug cocktails. A cocktail is a mixture of any one of the compounds useful with this invention with another drug or agent. In this embodiment, a common administration vehicle (e.g., pill, tablet, implant, pump, injectable solution, etc.) would contain both the instant composition in combination supplementary potentiating agent. The individual drugs of the cocktail are each administered in therapeutically effective amounts. A therapeutically effective amount will be determined by the parameters described above; but, in any event, is that amount which establishes a level of the drugs in the area of body where the drugs are required for a period of time which is effective in attaining the desired effects.

[0073] The practice of the present invention employs, unless otherwise indicated, conventional techniques of chemistry, molecular biology, microbiology, recombinant DNA, genetics, immunology, cell biology, cell culture and transgenic biology, which are within the skill of the art. See, e.g., Maniatis *et al.*, 1982; Sambrook *et al.*, 1989; Ausubel *et al.*, 1992; Glover, 1985; Anand, 1992; Guthrie and Fink, 1991; Harlow and Lane, 1988; Jakoby and Pastan, 1979; *Nucleic Acid Hybridization* (B. D. Hames & S. J. Higgins eds. 1984);

Transcription And Translation (B. D. Hames & S. J. Higgins eds. 1984); *Culture Of Animal Cells* (R. I. Freshney, Alan R. Liss, Inc., 1987); *Immobilized Cells And Enzymes* (IRL Press, 1986); B. Perbal, *A Practical Guide To Molecular Cloning* (1984); the treatise, *Methods In Enzymology* (Academic Press, Inc., N.Y.); *Gene Transfer Vectors For Mammalian Cells* (J. H. Miller and M. P. Calos eds., 1987, Cold Spring Harbor Laboratory); *Methods In Enzymology*, Vols. 154 and 155 (Wu et al. eds.), *Immunochemical Methods In Cell And Molecular Biology* (Mayer and Walker, eds., Academic Press, London, 1987); *Handbook Of Experimental Immunology*, Volumes I-IV (D. M. Weir and C. C. Blackwell, eds., 1986); Riott, *Essential Immunology*, 6th Edition, Blackwell Scientific Publications, Oxford, 1988; Hogan et al., Manipulating the Mouse Embryo, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986).

EXAMPLES

[0074] The present invention is described by reference to the following Examples, which are offered by way of illustration and are not intended to limit the invention in any manner. Standard techniques well known in the art or the techniques specifically described below were utilized.

EXAMPLE 1

Isolation of ω-Conotoxins

[0075] Crude venom was extracted from venom ducts (Cruz et al., 1976), and the components were purified as previously described (Cartier et al., 1996). The crude extract from venom ducts was purified by reverse phase liquid chromatography (RPLC) using a Vydac C_{18} semi-preparative column (10 x 250 mm). Further purification of bioactive peaks was done on a Vydac C_{18} analytical column (4.6 x 220 mm). The effluents were monitored at 220 nm. Peaks were collected, and aliquots were assayed for activity. Throughout purification, HPLC fractions were assayed by means of intracerebral ventricular (i.c.v.) injection into mice (Clark et al., 1981).

[0076] The amino acid sequence of the purified peptides were determined by standard methods. The purified peptides were reduced and alkylated prior to sequencing by automated Edman degradation on an Applied Biosystems 477A Protein Sequencer with a 120A Analyzer (DNA/Peptide Facility, University of Utah) (Martinez et al., 1995; Shon et al., 1994).

[0077] In accordance with this method, the ω-conopeptides described as "isolated" in Table 1 were obtained. These ω-conopeptides, as well as the other ω-conopeptides and the ω-conopeptide precursors set forth in Table 1 are synthesized as described in U.S. Patent No. 5,591,821.

EXAMPLE 2

Isolation of DNA Encoding ω-Conopeptides

[0078] DNA coding for ω-conopeptides was isolated and cloned in accordance with conventional techniques using general procedures well known in the art, such as described in Olivera et al. (1996). Alternatively, cDNA libraries was prepared from *Conus* venom duct using conventional techniques. DNA from single clones was amplified by conventional techniques using primers which correspond approximately to the M13 universal priming site and the M13 reverse universal priming site. Clones having a size of approximately 300-500 nucleotides were sequenced and screened for similarity in sequence to known ω-conotoxins. The DNA sequences and encoded propeptide sequences are set forth in Table 1. DNA sequences coding for the mature toxin can also be prepared on the basis of the DNA sequences set forth in Table1. An alignment of the ω-conopeptides of the present invnetion is set forth in Table 2.

TABLE 1

DNA and Amino Acid Sequences of ω-Conopeptides and Precursors

Name: J410

Species:

Cloned: Yes

DNA Sequence:

GGATCCATGAAACTGACGTGCATGGTGATCGTCGCCGTGCTGCTCCTGACGGCCTGT
CAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATCATGCCCTGAGGTC
GACCACCAATTTCTCCACGTTGACTCGTCGCTGCCTTTCTCCCGGATCACGATGTCA
TAAGACAATGCGTAACTGCTGCACTTCATGCTCTTCATACAAAGGGAAATGTCGGCC
TCGAAAATGAACCACTCATCACCTACTCCTCTGGAGGCCTCAGAGGAATTACATTGA
AATAAAAGCCGCATTACAAAAAAAAAAAAAAAAA (SEQ ID NO:1)

Translation:

MKLTCMVIVAVLLLTACQLITADDSRGTQKHHALRSTTNFSTLTRRCLSPGSRCHKTMR
NCCTSCSSYKGKCRPRK (SEQ ID NO:2)

Toxin Sequence:
Cys-Leu-Ser-Xaa3-Gly-Ser-Arg-Cys-His-Lys-Thr-Met-Arg-Asn-Cys-Cys-Thr-Ser-Cys-Ser-Ser-Xaa5-Lys-Gly-Lys-Cys-Arg-Xaa3-Arg-Lys-^ (SEQ ID NO:3)

Name: J411
Species:
Cloned: Yes

DNA Sequence:
GGATCCATGAAACTGACGTGCGTGGTGATCGTCGCCGTGCTGCTCCTGACGGTCTGT
CAACTCATCACAGCTGATGACTCCAGAGGTACGGCAGAAGCATCATGCCCTGAGGTC
GACCACCAATTTCTCCACGTCGACTCGTCGCTGCAAACCTCCCGGAAGAAAATGTCT
GAATAGAAAGAATGAATGCTGCAGCAAGTTTTGCAATGAACACCTACATATGTGTG
GATAAATGGCTAAAAACTGAATAAAAGCCGCATTGCAAAAAAAAAAAAAAAAAAAA
AA (SEQ ID NO:4)

Translation:
MKLTCVVIVAVLLLTVCQLITADDSRGTQKHHALRSTTNFSTSTRRCKPPGRKCLNRKN
ECCSKFCNEHLHMCG (SEQ ID NO:5)

Toxin Sequence:
Cys-Lys-Xaa3-Xaa3-Gly-Arg-Lys-Cys-Leu-Asn-Arg-Lys-Asn-Xaa1-Cys-Cys-Ser-Lys-Phe-Cys-Asn-Xaa1-His-Leu-His-Met-Cys-# (SEQ ID NO:6)

Name: J413
Species:
Cloned: Yes

DNA Sequence:
GGATCCATGAAACTGACGTGCGTGGTGATCGTCGCCGTGCTGCTCCTGACGGCCTGT
CAACTCGTCACAGCTGATGGCTCCAGAGGTATGCAGAAGCATTATGCCCTGAGGTC
GACCACCAATCTCTCCATATCGTCTCGCTGCAAACCTCCCAGAAGAAAATGTCTGAA
GATTAAGGATAAATGCTGCAACTTTTGCAATACACACCTAAATATGTGTGGATAAAT
GGCTAAAAACTGAATAAAAGCCGCATTGCAAAAAAAAAAAAAAAAAAAAA (SEQ ID NO:7)

Translation:
MKLTCVVIVAVLLLTACQLVTADGSRGMQKHYALRSTTNLSISSRCKPPRRKCLKIKDK
CCNFCNTHLNMCG (SEQ ID NO:8)

Toxin Sequence:
Cys-Lys-Xaa3-Xaa3-Arg-Arg-Lys-Cys-Leu-Lys-Ile-Lys-Asp-Lys-Cys-Cys-Asn-Phe-Cys-Asn-Thr-His-Leu-Asn-Met-Cys-# (SEQ ID NO:9)

Name: J414
Species:
Cloned: Yes

DNA Sequence:
GGATCCATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCTCCTGATGGCCTGT
CAACTCGTCACAGCTGATGGCTCCAGAGGTATGCACAAGCATTATGCCCTGAGGTC
GACCACCAAACTCTCCATGTCGACTCGCTGCGCAGGTCCAGGAACAATTTGTCCTAA
TAGGGTATGCTGCGGTTATTGCAGTAAAAGAACACATCTATGTCATTCGCGAACTGG
CTGATCTTCCCCCTTCTGCGCTCCATCCTTTTCTGCCTGAGTCCTCCATACCTGAGAA
TGGTCATGAACCACTCAACACCTACTCCTCTGGAGGGCCTCAGAAGAGCTACATTG
AAATAAAAGCCGCATTACAAAAAAAAAAAAAAAAAAAAA (SEQ ID NO:10)

Translation:
MKLTCVVIVAVLLLMACQLVTADGSRGMHKHYALRSTTKLSMSTRCAGPGTICPNRVC
CGYCSKRTHLCHSRTG (SEQ ID NO:11)

Toxin Sequence:
Cys-Ala-Gly-Xaa3-Gly-Thr-Ile-Cys-Xaa3-Asn-Arg-Val-Cys-Cys-Gly-Xaa5-Cys-Ser-Lys-Arg-Thr-His-Leu-Cys-His-Ser-Arg-Thr-# (SEQ ID NO:12)

Name: Ar6.10
Species: arenatus
Cloned: Yes

DNA Sequence:
GGATCCATGAAACTGACGTGCATGGTGATCATCGCCGTGCTGTTCCTGACGGCCTGT
CAACTCATTACAGGTGAGCAGAAGGACCATGCTCTGAGGTCAACTGACAAAAACTC
CAAGTTGACTAGGCAGTGCTCGGCTAACGGTGGATCTTGTACTCGTCATTTTCACTG
CTGCAGCCTCTATTGCAATAAAGATTCCAGTGTATGTGTGGCAACCTCATACCCGTG
AGTGGCCATGAACCCCTCAATACCCTCTCCTCTGGAGGCTTCAGAGGAACTGCATTG
AAATAAAACCGCATTGCAATAAAAAAAAAAAAAAAAAAA (SEQ ID NO:13)

Translation:
MKLTCMVIIAVLFLTACQLITGEQKDHALRSTDKNSKLTRQCSANGGSCTRHFHCCSLY
CNKDSSVCVATSYP (SEQ ID NO:14)

Toxin Sequence:
Xaa2-Cys-Ser-Ala-Asn-Gly-Gly-Ser-Cys-Thr-Arg-His-Phe-His-Cys-Cys-Ser-Leu-Xaa5-Cys-Asn-Lys-Asp-Ser-Ser-Val-Cys-Val-Ala-Thr-Ser-Xaa5-Xaa3-^ (SEQ ID NO:15)

Name: Ar6.2
Species: arenatus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGCGTGTTGATTATCGCCGTGCTGTTC
CTGACGGCCTGTCAACTCATTACAGCTGAGACTTACTCCAGAGGTGAGCAGAAGCA
CCATGCTCTGAGGTCAACTGACAGAAACTCCAAGTTGACCAGGACATGCAACACTC
CCACTGAATATTGTACTTTGCATCGACACTGCTGCAGCGGCTACTGCCATAAAACAA
TCCAGGCATGTTCATAATACCGGTGAGTGGTCATGAACCACTCAATACCCTCTCCTC
TGGAGGCTTCAGAGGAACTGCATTGAAATAAAAGCCGCATTGC (SEQ ID NO:16)

Translation:
MKLTCVLIIAVLFLTACQLITAETYSRGEQKHHALRSTDRNSKLTRTCNTPTEYCTLHRH
CCSGYCHKTIQACS (SEQ ID NO:17)

Toxin Sequence:
Thr-Cys-Asn-Thr-Xaa3-Thr-Xaa1-Xaa5-Cys-Thr-Leu-His-Arg-His-Cys-Cys-Ser-Gly-Xaa5-
Cys-His-Lys-Thr-Ile-Gln-Ala-Cys-Ser-^ (SEQ ID NO:18)

Name: Ar6.3
Species: arenatus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGCGTGTTGATCATCGCCGTGCTGTTC
CTGACGGCCTGTCAACTCATTACAGCTGAGACTTACTCCAGAGGTGAGCAGATGCA
CCGTGCTCTGAGGTCAACTGACAAAAACTCCAAGTTGACTAGGCAGTGCACGCCTA
ACGGTGGATCTTGTTCTCGTCATTTTCACTGCTGCAGCCTCTATTGCAATAAAAGTA
CTGGCGTATGTATTGCAACCTCATACCCGTGAGTGGTCATGAACCACTCAATACCCT
CTCCTCTGGAGGCTTCAGAGGAACTGCATTGAAATAAAAGCCGCATTGC (SEQ ID
NO:19)

Translation:
MKLTCVLIIAVLFLTACQLITAETYSRGEQMHRALRSTDKNSKLTRQCTPNGGSCSRHF
HCCSLYCNKSTGVCIATSYP (SEQ ID NO:20)

Toxin Sequence:
Xaa2-Cys-Thr-Xaa3-Asn-Gly-Gly-Ser-Cys-Ser-Arg-His-Phe-His-Cys-Cys-Ser-Leu-Xaa5-Cys-
Asn-Lys-Ser-Thr-Gly-Val-Cys-Ile-Ala-Thr-Ser-Xaa5-Xaa3-^ (SEQ ID NO:21)

Name: Ar6.4
Species: arenatus
Cloned: Yes

DNA Sequence:
GGATCCATGAAACTGACGTGCATGGTGATTATCGCCGTGCTGTTCCTGACGGCCTGT
CAACTCATTACAGCTGAGACTTACTCCAGAGGTGAGCAGAAGCACCATGCTCTGAG
GTCAACTGACAAAAACTCCAAGTTGACCAGGACATGCAACACTCCCACCGAATATT

GTACTTTGCATCAACACTGCTGCAGCGGCTACTGCCATAAAACAATCCAGGCATGTT
CATAATACCGGTGAGTGGTCATGAACCACTCAATACCCTCTCCTCTGGAGGCTTCAG
AGGAACTGCATTGAAATAAAACCGCATTACAAAAAAAAAAAAAAAAAAAA (SEQ ID NO:22)

Translation:
MKLTCMVIIAVLFLTACQLITAETYSRGEQKHHALRSTDKNSKLTRTCNTPTEYCTLHQ HCCSGYCHKTIQACS (SEQ ID NO:23)

Toxin Sequence:
Thr-Cys-Asn-Thr-Xaa3-Thr-Xaa1-Xaa5-Cys-Thr-Leu-His-Gln-His-Cys-Cys-Ser-Gly-Xaa5-Cys-His-Lys-Thr-Ile-Gln-Ala-Cys-Ser-^ (SEQ ID NO:24)

Name: Ar6.6
Species: arenatus
Cloned: Yes

DNA Sequence:
GGATCCATGAAACTGACGTGTATGGTGATCATCGCCGTACTGTTCCTGACGGCCTGT
CAACTCATTACAGCTGAGACTTACTCCAGAGGTAAGCAGATGCACCGCGCTCTGAG
GTCAACTGACAAAAACTCCCAGTTGACCAGGGAATGCACACCTCCCGGTGGAGCTT
GTGGTTTACCTACACACTGCTGCGGGTTTTGCGATACTGCAAACAACAGATGTCTGT
AAAGCTGGTCTGGCGTCTGATATTCCCCTTCTGTGCTCTATCCTCTTTGGCCTGAGTC
ATCCGTACCTGTGAGTGGTCATGAACTACTCAATACCCTCTCCTCTGGAGGCTTCAG
AGGAACTACAATGAAATAAAACCCGCATTGCAGAGAAAAAAAAAAAAAAAAAAA
(SEQ ID NO:25)

Translation:
MKLTCMVIIAVLFLTACQLITAETYSRGKQMHRALRSTDKNSQLTRECTPPGGACGLPT HCCGFCDTANNRCL (SEQ ID NO:26)

Toxin Sequence:
Xaa1-Cys-Thr-Xaa3-Xaa3-Gly-Gly-Ala-Cys-Gly-Leu-Xaa3-Thr-His-Cys-Cys-Gly-Phe-Cys-Asp-Thr-Ala-Asn-Asn-Arg-Cys-Leu-^ (SEQ ID NO:27)

Name: Ar6.7
Species: arenatus
Cloned: Yes

DNA Sequence:
GGATCCATGAAACTGACGTGCGTGGTGATTATCGCCGTGCTGTTCCTGACGGCCTGT
CAACTCATTACAGCTGAGACTTACTCCAGAGGTGAGCAGAATCACCATGTTCTGAG
GTCAACTGACAAAAACTCCAAGTTGACCAGGACATGCAACACTCCCACTGAATATT
GTACTTTGCATCAACACTGCTGCAGCGGCCACTGCCATAAAACAATCCAGGCATGT
GCATAATACCGGTGGGTGGTCATGAACCACTCAATACCCTCTCCTCTGGAGGCTTCA

GAGGAACTGCATTGAAATAAAACCGCATTGCAATGAANAAAAAAAAAAAAAAAAAA
AAAAAAAA (SEQ ID NO:28)

Translation:

MKLTCVVIIAVLFLTACQLITAETYSRGEQNHHVLRSTDKNSKLTRTCNTPTEYCTLHQ
HCCSGHCHKTIQACA (SEQ ID NO:29)

Toxin Sequence:

Thr-Cys-Asn-Thr-Xaa3-Thr-Xaa1-Xaa5-Cys-Thr-Leu-His-Gln-His-Cys-Cys-Ser-Gly-His-Cys-
His-Lys-Thr-Ile-Gln-Ala-Cys-Ala-^ (SEQ ID NO:30)

Name: Ar6.8
Species: arenatus
Cloned: Yes

DNA Sequence:

GGATCCATGAAACTGACGTGTGTGGTGATCATCGCCGTGCTGTTCCTGACGGCCTGT
CAACTCACTACAGGTGAGCAGAAGGACCATGCTCTGAGGTCAACTGACAAAAACTC
CAAGTTGACTAGGCAGTGCTCGCCTATCGGTGGATATTGTACTCTTCATATTCACTG
CTGCAGCAACCATTGCATTAAACCTATCGGCCGATGTGTGGCAACCTGATACCCGTG
CGTGGTCATGAACCCCTCAATACCCTCTCCTCTGGAGGCTTCAGAGGAACTGCATTG
AAATAAAACCGCATTGCAATAAAAAAAAAAAAAAAAAA (SEQ ID NO:31)

Translation:

MKLTCVVIIAVLFLTACQLTTGEQKDHALRSTDKNSKLTRQCSPIGGYCTLHIHCCSNHC
IKPIGRCVAT (SEQ ID NO:32)

Toxin Sequence:

Xaa2-Cys-Ser-Xaa3-Ile-Gly-Gly-Xaa5-Cys-Thr-Leu-His-Ile-His-Cys-Cys-Ser-Asn-His-Cys-Ile-
Lys-Xaa3-Ile-Gly-Arg-Cys-Val-Ala-Thr-^ (SEQ ID NO:33)

Name: Ar6.9
Species: arenatus
Cloned: Yes

DNA Sequence:

GGATCCATGAAACTGACGTGCGTGGTGATCATCGCCGTGCTGTTCCTGACGGCCTGT
CAACTCACTACAGGTGAGCAGAAGGACCATGCTCTGAGGTCAACTGACAAAAACTC
CAAGTTGACTAGGCAGTGCTTGCCTAACGGTGGATATTGTACTCTTCATATTCACTG
CTGCAGCGACCATTGCATTAAACCTATCGACCGATGTGTGGCAACCTGATACCCGG
GCGTGGTCATGAACCCCTCAATACCCTCTCCTCTGGAGGCTTCAGAGGAACTGCATT
GAAATAAAACCGCATTACAAAAAAAAAAAAAAAAAA (SEQ ID NO:34)

Translation:

MKLTCVVIIAVLFLTACQLTTGEQKDHALRSTDKNSKLTRQCLPNGGYCTLHIHCCSDH
CIKPIDRCVAT (SEQ ID NO:35)

Toxin Sequence:
Xaa2-Cys-Leu-Xaa3-Asn-Gly-Gly-Xaa5-Cys-Thr-Leu-His-Ile-His-Cys-Cys-Ser-Asp-His-Cys-
Ile-Lys-Xaa3-Ile-Asp-Arg-Cys-Val-Ala-Thr-^ (SEQ ID NO:36)

Name: Ay6.1
Species: aurisiacus
Cloned: Yes

DNA Sequence:
ATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCTCCTGACGGCCTGTCAACTC
ATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATCGTTCCCTGAGCTCGGCCAC
CAAACTCTCCATGTCGACTCGCTGCAAGGGTAAAGGAAAACCATGCAGTAGGATTT
CGTATAACTGCTGCACCGGTTCTTGCAGATCAGGTAAATGTGGCTGATCCAGCGCCT
GATCTTCCCCCTTCTGTGCTCTATCCTTTTCTGCCTGAGTCCTCCTTACCTGAGAGTG
GTCATGAACCACTCATCACCTGCTCCTCTGGAGGCCCCAGAGGAGCTACATTGAAAT
AAAAGTCGCATTGCAAAAAAAAAAAAAAAAAAA (SEQ ID NO:37)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQKHRSLSSATKLSMSTRCKGKGKPCSRISYN
CCTGSCRSGKCG (SEQ ID NO:38)

Toxin Sequence:
Cys-Lys-Gly-Lys-Gly-Lys-Xaa3-Cys-Ser-Arg-Ile-Ser-Xaa5-Asn-Cys-Cys-Thr-Gly-Ser-Cys-
Arg-Ser-Gly-Lys-Cys-# (SEQ ID NO:39)

Name: Ay6.2
Species: aurisiacus
Cloned: Yes

DNA Sequence:
ATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCTCCTGACGGCCTGTCAACTC
ATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATCGTTCCCTGAGGTCGAAGAC
CAAACTCTCCATGTCGACTGGCTGCATGGAAGCCGGATCTTATTGCGGCTCTACTAC
GAGAATCTGCTGCGGTTTTTGCGCTTATTTCGGCAAAAAATGTATTGACTATCCCAG
CAACTGATCTTCCCCCTACTGTGCTCTATCCTTTTCTGCCTGAGTCCTCCTTACCTGA
GAGTGGTCATGAACCACTCATCACCTGCTCCTCTGGAGGCCCCAGAGGAGCTACATT
GAAATAAAATCGCATTGCTAAAAAAAAAAAAAAAAAAA (SEQ ID NO:40)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQKHRSLRSKTKLSMSTGCMEAGSYCGSTTRI
CCGFCAYFGKKCIDYPSN (SEQ ID NO:41)

Toxin Sequence:
Cys-Met-Xaa1-Ala-Gly-Ser-Xaa5-Cys-Gly-Ser-Thr-Thr-Arg-Ile-Cys-Cys-Gly-Phe-Cys-Ala-Xaa5-Phe-Gly-Lys-Lys-Cys-Ile-Asp-Xaa5-Xaa3-Ser-Asn-^ (SEQ ID NO:42)

Name: Ay6.3
Species: aurisiacus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATC
GTTCCCTGAGCTCGGCCACCAAACTCTCCATGTCGACTCGCTGCAAGGCTAAAGGA
AAACCATGCAGTAGGATTGCGTATAACTGCTGCACCGGTTCTTGCAGATCAGGTAA
ATGTGGCTGATCCAGTGCCTGATCTTCCCCCTTCTGTGCTCTATCCTTTTCTGCCTGA
GTCCTCCTTACCTGAGAGTGGTCATGAACCACTCATCACCTGCTCCTCTGGAGGCCC
CAGAGGAGCTACATTGAAATAAAAGCCGCATTGC (SEQ ID NO:43)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQKHRSLSSATKLSMSTRCKAKGKPCSRIAYN
CCTGSCRSGKCG (SEQ ID NO:44)

Toxin Sequence:
Cys-Lys-Ala-Lys-Gly-Lys-Xaa3-Cys-Ser-Arg-Ile-Ala-Xaa5-Asn-Cys-Cys-Thr-Gly-Ser-Cys-Arg-Ser-Gly-Lys-Cys-# (SEQ ID NO:45)

Name: Ay6.4
Species: aurisiacus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGACCTGTCAACTCATCACAGCTGATGACTCCAGAGGTACGCAGGAGCATC
GTGCCCTGAGGTCGAAGACAAAACTCTCCATGTTAACTTTGCGCTGCGCATCTTACG
GAAAACCTTGTGGTATTGACAACGACTGCTGCAATGCATGCGATCCAGGAAGAAAT
ATATGTACGTAGCTGATCCAGCGCCTGATCTTCCCCCTTCTGTGCTCTATCCTTTTCT
GCCCGAGTCCTCCTTACCTGAGAGTGGTCATGAACCACTCATCACCTGCTCCCTGGA
GGCCTCAGAGGAGCTACAATGAAATAAAAGCCGCATTGC (SEQ ID NO:46)

Translation:
MKLTCVVIVAVLLLTTCQLITADDSRGTQEHRALRSKTKLSMLTLRCASYGKPCGIDND
CCNACDPGRNICT (SEQ ID NO:47)

Toxin Sequence:
Cys-Ala-Ser-Xaa5-Gly-Lys-Xaa3-Cys-Gly-Ile-Asp-Asn-Asp-Cys-Cys-Asn-Ala-Cys-Asp-Xaa3-

Gly-Arg-Asn-Ile-Cys-Thr-^ (SEQ ID NO:48)

Name: Bu6.1
Species: bullatus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGCGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAGCTCATTACAGCTGAAGACTCCAGAGGTACGCATGAGCATC
TTGCCCTGAAGTCGACCTCCAAAGTCTCCAAGTCGACTAGCTGCATGGAAGCCGGA
TCTTATTGCGGACCTGCTACTACGAAAATCTGCTGCGATTTTTGCAGTCCATTCAGC
GATAGATGTATGAACAATCCCAACAATTGATCTTCCCCCTTGTGTGCTCCATCCTTTT
CTGCCTGAGTCCTCCTTACCTGAGAGTGGTCATGAACCACTCATCACCTACTCCTCT
GGAGGCTTCAGAGGAGCTACATTGAAATAAAAGCCGCATTGC (SEQ ID NO:49)

Translation:
MKLTCVAIVAVLLLTACQLITAEDSRGTHEHLALKSTSKVSKSTSCMEAGSYCGPATTK
ICCDFCSPFSDRCMNNPNN (SEQ ID NO:50)

Toxin Sequence:
Ser-Thr-Ser-Cys-Met-Xaa1-Ala-Gly-Ser-Xaa5-Cys-Gly-Xaa3-Ala-Thr-Thr-Lys-Ile-Cys-Cys-
Asp-Phe-Cys-Ser-Xaa3-Phe-Ser-Asp-Arg-Cys-Met-Asn-Asn-Xaa3-Asn-Asn-^ (SEQ ID NO:51)

Name: Bu6.2
Species: bullatus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAGCTCATTACAGCTGAAGACTCCAGAGGTACGCAGTTGCATC
GTGCCCTGAGGAAGGCCACCAAACACCCTGTGTCGACTCGCTGCATTACTCCAGGA
ACACGATGTAAGGTTCCGAGCCAATGCTGCAGAGGTCCTTGCAAGAACGGTCGTTG
TACTCCATCCCCTTCTGAATGGTAAATGTGGTTGATCCAGCGCCTGATCTTCCCCCTT
CGTCGTGCTCCATCCTTTTCTGCCTGAGTCCTCCTTACCTGAGAGTGGTCATGAACC
ACTCATCACCTACTCCCCTGGAGGCTTCAGAGGAGCTACATTGAAATAAAAGCCGC
ATTGC (SEQ ID NO:52)

Translation:
MKLTCVVIVAVLLLTACQLITAEDSRGTQLHRALRKATKHPVSTRCITPGTRCKVPSQC
CRGPCKNGRCTPSPSEW (SEQ ID NO:53)

Toxin Sequence:
Cys-Ile-Thr-Xaa3-Gly-Thr-Arg-Cys-Lys-Val-Xaa3-Ser-Gln-Cys-Cys-Arg-Gly-Xaa3-Cys-Lys-
Asn-Gly-Arg-Cys-Thr-Xaa3-Ser-Xaa3-Ser-Xaa1-Xaa4-^ (SEQ ID NO:54)

Name: Bu6.3
Species: bullatus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGCGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAGCTCATTACAGCTGAGGACTCCAGAGATACGCAGAAGCATC
GTGCCCTGAGGTCGGACACCAAACTCTCCATGTTGACTTTGCGCTGCGCAACTTACG
GAAAACCTTGTGGTATTCAAAACGACTGCTGCAATACATGCGATCCAGCCAGAAGG
ACATGTACGTAGCTGATCCGGCGTCTTGATCCTCCGCTTCTGTGCTCCATCTTTTCTG
CCTGAGTCCTCCTTACCTGAGAGTGGTCATGAACCACTCATCACCTACTCCTCTGGA
GGCTTTAGAGGAGCTACATTGAAATAAAAGCCGCATTGC (SEQ ID NO:55)

Translation:
MKLTCVAIVAVLLLTACQLITAEDSRDTQKHRALRSDTKLSMLTLRCATYGKPCGIQND
CCNTCDPARRTCT (SEQ ID NO:56)

Toxin Sequence:
Cys-Ala-Thr-Xaa5-Gly-Lys-Xaa3-Cys-Gly-Ile-Gln-Asn-Asp-Cys-Cys-Asn-Thr-Cys-Asp-Xaa3-
Ala-Arg-Arg-Thr-Cys-Thr-^ (SEQ ID NO:57)

Name: Bu6.4
Species: bullatus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGCGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAGCTCATTACAGCTGAAGACTCCAGAGGTACGCAGTTGCATC
GTGCCCTGAGGAAGACCACCAAACTCTCCTTGTCGACTCGCTGCAAGGGTCCAGGA
GCATCATGTATAAGGATTGCGTATAACTGCTGCAAGTATTCTTGCAGAAATGGTAAA
TGTGGCTGATCCAGCGCCTGATCTTCCCCCTTGTGTGCTCCATCCTTTTCTGCCTGAG
TCCTCCTTACCTGAGAGTGGTCATGAACCACTCATCACCTACTCCTCTGGAGGCTTC
AGAGGAGCTACATTGAAATAAAAGCCGCATTGC (SEQ ID NO:58)

Translation:
MKLTCVAIVAVLLLTACQLITAEDSRGTQLHRALRKTTKLSLSTRCKGPGASCIRIAYNC
CKYSCRNGKCG (SEQ ID NO:59)

Toxin Sequence:
Cys-Lys-Gly-Xaa3-Gly-Ala-Ser-Cys-Ile-Arg-Ile-Ala-Xaa5-Asn-Cys-Cys-Lys-Xaa5-Ser-Cys-
Arg-Asn-Gly-Lys-Cys-# (SEQ ID NO:60)

Name: Bu6.5
Species: bullatus
Cloned: Yes

DNA Sequence:
ATCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCTC
CTGACGGCCTGTCAGCTCATTACAGCTGAAGACTCCAGAGGTACGCATGAGCATCTT
GCCCTGAAGTCGACCTCCAAAGTCTCCAAGTCGACTAGCTGCATGGCAGCCGGATC
TTATTGCGGACCTGCTACTACGAATATCTGCTGCGATTTTTGCAGTCCATTCAGCGA
TAGATGTATGAAAAAGCCCAACAATTGATCTTCCCCCTTCTGTGCTCTATCCTTTTCT
GCCTGAGTCCTCCTTACCTGAGAGTGGTCATGAACCACTCATCACCTACTCCTCTGG
AGGCTTCAGAGGAGCTACATTGAAATAAAAGCCGCATTGC (SEQ ID NO:61)

Translation:
MKLTCVVIVAVLLLTACQLITAEDSRGTHEHLALKSTSKVSKSTSCMAAGSYCGPATTN
ICCDFCSPFSDRCMKKPNN (SEQ ID NO:62)

Toxin Sequence:
Ser-Thr-Ser-Cys-Met-Ala-Ala-Gly-Ser-Xaa5-Cys-Gly-Xaa3-Ala-Thr-Thr-Asn-Ile-Cys-Cys-
Asp-Phe-Cys-Ser-Xaa3-Phe-Ser-Asp-Arg-Cys-Met-Lys-Lys-Xaa3-Asn-Asn-^ (SEQ ID NO:63)

Name: Bu6.6
Species: bullatus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAGCTCATTATAGCTGAGGACTCCAGAGGTACGCAGTTGCATCG
TGCCCTGAGGAAGGCCACCAAACTCTCCGTGTCGACTCGCTGCAAGAGTAAAGGAT
CATCATGTCATAGGACTTCGTATGACTGCTGCACGGGTTCTTGCAGAAATGGTAGAT
GTGGCTGATCCAGCGCCTGATCTTCCCCCTTCTGTGCTCCATCCTTTTCTGCCTGAGT
CCTCCTTACCTGAGAGTGGTCATGAACCACTCATCACCTACTCCTCTGGAGGCTTCA
GAGGAGCTACATTGAAATAAAAGCCGCATTGC (SEQ ID NO:64)

Translation:
MKLTCVVIVAVLLLTACQLIIAEDSRGTQLHRALRKATKLSVSTRCKSKGSSCHRTSYD
CCTGSCRNGRCG (SEQ ID NO:65)

Toxin Sequence:
Cys-Lys-Ser-Lys-Gly-Ser-Ser-Cys-His-Arg-Thr-Ser-Xaa5-Asp-Cys-Cys-Thr-Gly-Ser-Cys-Arg-
Asn-Gly-Arg-Cys-# (SEQ ID NO:66)

Name: Ca6.4
Species: caracteristicus
Cloned: Yes

DNA Sequence:
GGATCCATGAAACTGACGTGCGTGGTGATCATCGCCGTGCTGTTCCTGACGGCCTGT
CAACTCATTACAGGTGAGCAGAAGGACCATGCTCTGAGGTCAACTGACAAAAACTC
CAAGTTGACTAGGCAGTGCTCGGCTAACGGTGGATCTTGTACTCGTCATTTTCACTG
CTGCAGCCTCTATTGCAATAAAGATTCCAGTGTATGTGTGGCAACCTCATACCCGTG
AGTGGCCATGAACCCCTCAATACCCTCTCCTCTGGAGGCTTCAGAGGAACTGCATTG
AAATAAAACCGCATTACAAAAAAAAAAAAAAAAAAAA (SEQ ID NO:67)

Translation:
MKLTCVVIIAVLFLTACQLITGEQKDHALRSTDKNSKLTRQCSANGGSCTRHFHCCSLY
CNKDSSVCVATSYP (SEQ ID NO:68)

Toxin Sequence:
Xaa2-Cys-Ser-Ala-Asn-Gly-Gly-Ser-Cys-Thr-Arg-His-Phe-His-Cys-Cys-Ser-Leu-Xaa5-Cys-Asn-Lys-Asp-Ser-Ser-Val-Cys-Val-Ala-Thr-Ser-Xaa5-Xaa3-^ (SEQ ID NO:69)

Name: C6.1
Species: catus
Cloned: Yes

DNA Sequence:

Translation:
CKSTGASCRRTSYDCCTGSCRSGRCG (SEQ ID NO:70)

Toxin Sequence:
Cys-Lys-Ser-Thr-Gly-Ala-Ser-Cys-Arg-Arg-Thr-Ser-Xaa5-Asp-Cys-Cys-Thr-Gly-Ser-Cys-Arg-Ser-Gly-Arg-Cys-# (SEQ ID NO:71)

Name: C6.4
Species: catus
Cloned: Yes

DNA Sequence:
TCGACTCGCTGCCAGGGTAGAGGAGCATCATGTCGTAAGACTATGTATAACTGCTG
CAGCGGTTCTTGCAACAGAGGTAGTTGTGGCTGATCCGGCGCCTGATCTTCCCCCTT
CCGTGCTCTATCCTTTTCTGCCTGATTCCTCCTTACCTGAGAGCGGTCATGAACCACT
CATCACCTGCTCCTCTGGAGGCCTCAGAGGAGCTACATTGAAATAAAAGCCGCATT
GC (SEQ ID NO:72)

Translation:
STRCQGRGASCRKTMYNCCSGSCNRGSCG (SEQ ID NO:73)

Toxin Sequence:

Cys-Gln-Gly-Arg-Gly-Ala-Ser-Cys-Arg-Lys-Thr-Met-Xaa5-Asn-Cys-Cys-Ser-Gly-Ser-Cys-Asn-Arg-Gly-Ser-Cys-# (SEQ ID NO:74)

Name: C6.5
Species: catus
Cloned: Yes

DNA Sequence:
TCGACACGCTGCTTGCCTGCCGGAGAGTCTTGCCTTTTTAGTAGGATTAGATGCTGC
GGTACTTGCAGTTCAGTCTTAAAGTCATGTGTGAGCTGATCCAGCTGCTGATCTTCC
TCCTCCTGTGCTCCATCCTTTTCTGCCTGAGTCCTCCTTATCTGAGAGTGGTCATGAA
CCACTCACCACCTACTCTTCTGGAGGCTTCAGAGGAGCTACAGTGAAATAAAAGCC
GCATTGC (SEQ ID NO:75)

Translation:
STRCLPAGESCLFSRIRCCGTCSSVLKSCVS (SEQ ID NO:76)

Toxin Sequence:
Cys-Leu-Xaa3-Ala-Gly-Xaa1-Ser-Cys-Leu-Phe-Ser-Arg-Ile-Arg-Cys-Cys-Gly-Thr-Cys-Ser-Ser-Val-Leu-Lys-Ser-Cys-Val-Ser-^ (SEQ ID NO:77)

Name: C6.6
Species: catus
Cloned: Yes

DNA Sequence:
TCGACACGCTGCCAGGGTAGAGGAGGACCATGTACTAAGGCTGTGTTTAACTGCTG
CAGCGGTTCTTGCAACAGAGGTAGATGTGGCTGATCCAGCGCCTGATCTTCCCCCTT
CTGTGCTCTATCCTTTTCTGCCTGAGTCCTCCTTACTGAGAGTAGTCATGAACCACTC
ATCACCTACTCCTCTGGAGGCCTCAGAGAGCTACATTGAAATAAAAGCCGCATTGC
(SEQ ID NO:78)

Translation:
STRCQGRGGPCTKAVFNCCSGSCNRGRCG (SEQ ID NO:79)

Toxin Sequence:
Cys-Gln-Gly-Arg-Gly-Gly-Xaa3-Cys-Thr-Lys-Ala-Val-Phe-Asn-Cys-Cys-Ser-Gly-Ser-Cys-Asn-Arg-Gly-Arg-Cys-# (SEQ ID NO:80)

Name: C6.7
Species: catus
Cloned: Yes

DNA Sequence:

TTAACTTTGCGCTGCGCAACTTACGGAAAACCTTGTGGTATTCAAAACGACTGCTGC
AATACATGCGATCCAGCCAGAAAGACATGTACGTAGCTGATCCGGCGTCTGATCTC
CCCCCTTCTGTGCTCTATCCTTTTCTGCCTGAGTCCTCCTTACCTGAGAGTGGTCATG
AACCACTCATCACCTGCTCCTCTGGAGGCCTCGGGGGAGCTACATTGAAATAAAAG
CCGCATTGC (SEQ ID NO:81)

Translation:
LTLRCATYGKPCGIQNDCCNTCDPARKTCT (SEQ ID NO:82)

Toxin Sequence:
Cys-Ala-Thr-Xaa5-Gly-Lys-Xaa3-Cys-Gly-Ile-Gln-Asn-Asp-Cys-Cys-Asn-Thr-Cys-Asp-Xaa3-Ala-Arg-Lys-Thr-Cys-Thr-^ (SEQ ID NO:83)

Name: C6.8
Species: catus
Cloned: Yes

DNA Sequence:
TCGACTCGCTGCCGGGGTAGAGGAGGACCATGTACTAAGGCTATGTTTAACTGCTG
CAGCGGTTCTTGCAACAGAGGTAGATGTGGCTGATCCAGCGCCTGATCTTCCCCCTT
CTGTGCTCTATCCTTTTCTGCCTGAGTCCTCCTTAACTGAGAGTAGTCATGAACCACT
CATCACCTACTCCTCTGGAGGCCTCAGAGAAGCATCATTGAAATAAAAGCCGCATT
GC (SEQ ID NO:84)

Translation:
STRCRGRGGPCTKAMFNCCSGSCNRGRCG (SEQ ID NO:85)

Toxin Sequence:
Cys-Arg-Gly-Arg-Gly-Gly-Xaa3-Cys-Thr-Lys-Ala-Met-Phe-Asn-Cys-Cys-Ser-Gly-Ser-Cys-Asn-Arg-Gly-Arg-Cys-# (SEQ ID NO:86)

Name: Cr6.1
Species: circumcisus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGACCTGTCAACTCATCACAGCTGATGACTCCAGAGGTACGCAGGAGCATC
GTGCCCTGAGGTCGGACACCAAACTCCCCATGTCGACTCGCTGCAAGGGTAAAGGA
GCATCATGTCGTAAGACTATGTATAACTGCTGCAGCGGTTCTTGCAGCAACGGTAGA
TGTGGCTGATCCAGCGCCTGATCTTCCCCCTTCTGCTGCTCTATCCTTTTCTGCCTGA
GTCCTCCTTACCTGAGAGCTGGTCATGAACCACTCATCACCTGCTCCTCTGGAGGCC
CAGAGGAGCTACATTGAAATAAAAGCCGCATTGC (SEQ ID NO:87)

Translation:

MKLTCVVIVAVLLLTTCQLITADDSRGTQEHRALRSDTKLPMSTRCKGKGASCRKTMY
NCCSGSCSNGRCG (SEQ ID NO:88)

Toxin Sequence:
Cys-Lys-Gly-Lys-Gly-Ala-Ser-Cys-Arg-Lys-Thr-Met-Xaa5-Asn-Cys-Cys-Ser-Gly-Ser-Cys-Ser-Asn-Gly-Arg-Cys-# (SEQ ID NO:89)

Name: Cr6.2
Species: circumcisus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGACCTGTCAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATC
GTGCCCTGAGGTCGGCCACCAAAGTCTCCAAGTCGACTAGCTGCATGGAAGCCGGA
TCTTATTGCCGCTCTACTACGAGAACCTGCTGCGGTTATTGCTCTTATTTCAGCAAAA
AATGTATTGACTTTCCCAGCAACTGATCTTCCCCCTACTGTGCTCTATCCTTTTCTGC
CTGAGTCCTCCTTACCTGAGAGTGGTCATGAACCACTCATCACCCTACTCCTCTGGA
GGCCCAGAGGAGCTACATTGAAATAAAAGCCGCATTGC (SEQ ID NO:90)

Translation:
MKLTCVVIVAVLLLTTCQLITADDSRGTQKHRALRSATKVSKSTSCMEAGSYCRSTTRT
CCGYCSYFSKKCIDFPSN (SEQ ID NO:91)

Toxin Sequence:
Ser-Thr-Ser-Cys-Met-Xaa1-Ala-Gly-Ser-Xaa5-Cys-Arg-Ser-Thr-Thr-Arg-Thr-Cys-Cys-Gly-Xaa5-Cys-Ser-Xaa5-Phe-Ser-Lys-Lys-Cys-Ile-Asp-Phe-Xaa3-Ser-Asn-^ (SEQ ID NO:92)

Name: Cr6.3
Species: circumcisus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGACCTGTCAACTCATCACAGCTGATGACTCCAGAGGTACGCAGGAGCATC
GTGCCCTGAGGTCGGACACCAAACTCCCCATGTCGACTCGCTGCAAGAGTAAAGGA
GCAAAATGTTCAAGGCTTATGTATGACTGCTGCAGCGGTTCTTGCAGCAGGTACTCA
GGTAGATGTGGCTGATCCAGCGCCTGATCTTCCCCCTTCTGCTGCTCTATCCTTTTCT
GCCTGAGTCCTCCTTACCTGAGAGTGGTCATGAACCACTCATCACCTACTCCTCTGG
AGGCCCAGAGGAGCTACATTGAAATAAAAGCCGCATTGC (SEQ ID NO:93)

Translation:
MKLTCVVIVAVLLLTTCQLITADDSRGTQEHRALRSDTKLPMSTRCKSKGAKCSRLMY
DCCSGSCSRYSGRCG (SEQ ID NO:94)

Toxin Sequence:
Cys-Lys-Ser-Lys-Gly-Ala-Lys-Cys-Ser-Arg-Leu-Met-Xaa5-Asp-Cys-Cys-Ser-Gly-Ser-Cys-Ser-Arg-Xaa5-Ser-Gly-Arg-Cys-# (SEQ ID NO:95)

Name: Cr6.4
Species: circumcisus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGACCTGTCAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATC
GTTCCCTGACGTCGGCCACCAAAGTCTCCAAGTCGACTGGCTGCATGAAAGCCGGA
TCTTATTGCCGCTCTACTACGAGAACTTGCTGCGGTTATTGCGCTTATTTCGGCAAA
AAATGTATTGACTATCCCAGCAACTGATCTTCCCCCTACTGTGCTCTATCCTTTTCTG
CCTAAGTCCTCCTTACCTGAGAGTGGTCATGAACCACTCATCACCCTACTCCTCTGG
AGGCCCAGAGGAGCTACATTGAAATAAAAGCCGCATTGC (SEQ ID NO:96)

Translation:
MKLTCVVIVAVLLLTTCQLITADDSRGTQKHRSLTSATKVSKSTGCMKAGSYCRSTTRT
CCGYCAYFGKKCIDYPSN (SEQ ID NO:97)

Toxin Sequence:
Ser-Thr-Gly-Cys-Met-Lys-Ala-Gly-Ser-Xaa5-Cys-Arg-Ser-Thr-Thr-Arg-Thr-Cys-Cys-Gly-Xaa5-Cys-Ala-Xaa5-Phe-Gly-Lys-Lys-Cys-Ile-Asp-Xaa5-Xaa3-Ser-Asn-^ (SEQ ID NO:98)

Name: Cn6.1
Species: consors
Cloned: Yes

DNA Sequence:
ATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCTCCTGACGGCCTGTCAACTC
CTCACAGCTGATGACTCCAGAGGTACGCAGAAGCATCGTGCCCTGAAGTCTTACAC
CAAACTCTCCATGTTAACTTTGCGCTGCGCATCTTACGGAAAACCTTGTGGTATTGA
CAACGACTGCTGCAATACATGCGATCCAGCCAGAAAGACATGTACGTAGCTGATCC
GGCGTCTGATCTTCCCCCTTCTGTGCTCTATCCTTTTCTGCCTGAGTCCTCCTTACCT
GAGAGTGGTCATGAACCACTCATCACCTAGCTCCTCTGGAGGCTTCAGAGGAGCTA
CAATGAAATAAAAGCGCATTGC (SEQ ID NO:99)

Translation:
MKLTCVVIVAVLLLTACQLLTADDSRGTQKHRALKSYTKLSMLTLRCASYGKPCGIDN
DCCNTCDPARKTCT (SEQ ID NO:100)

Toxin Sequence:
Cys-Ala-Ser-Xaa5-Gly-Lys-Xaa3-Cys-Gly-Ile-Asp-Asn-Asp-Cys-Cys-Asn-Thr-Cys-Asp-Xaa3-Ala-Arg-Lys-Thr-Cys-Thr-^ (SEQ ID NO:101)

Name: Cn6.2
Species: consors
Cloned: Yes

DNA Sequence:
ATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCTCCTGACGGCCTGTCAACTC
CTCACAGCTGATGACTCCAGAGGTACGCAGAAGCATCGTGCCCTGAGGTCGGACAC
CAAACTCTCCATGTCGACTCGCTGCAAGGGTACAGGAAAACCATGCAGTAGGATTG
CGTATAACTGCTGCACCGGTTCTTGCAGATCAGGTAAATGTGGCTGATCCAGCGCCT
GATCTCCCCCC (SEQ ID NO:102)

Translation:
MKLTCVVIVAVLLLTACQLLTADDSRGTQKHRALRSDTKLSMSTRCKGTGKPCSRIAY
NCCTGSCRSGKCG (SEQ ID NO:103)

Toxin Sequence:
Cys-Lys-Gly-Thr-Gly-Lys-Xaa3-Cys-Ser-Arg-Ile-Ala-Xaa5-Asn-Cys-Cys-Thr-Gly-Ser-Cys-Arg-Ser-Gly-Lys-Cys-# (SEQ ID NO:104)

Name: Cn6.3
Species: consors
Cloned: Yes

DNA Sequence:
ATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCTCCTGACGGCCTGTCAACTC
ATCACAGCTGATGACTCCAAAGGTACGCAGAAGCATCGTTCCCTGAGGTCGACCAC
CAAAGTCTCCAAGGCGACTGACTGCATTGAAGCCGGAAATTATTGCGGACCTACTG
TTATGAAAATCTGCTGCGGCTTTTGCAGTCCATACAGCAAAATATGTATGAACTATC
CCCAAAATTGATCTTCCCCCTTCTGTGCTCTATCCTTTTCTGCCTGAGTCCTCCTTAC
CTGAGAGTGGTCATGAACCACTCATCACCTCGTCCC (SEQ ID NO:105)

Translation:
MKLTCVVIVAVLLLTACQLITADDSKGTQKHRSLRSTTKVSKATDCIEAGNYCGPTVM
KICCGFCSPYSKICMNYPQN (SEQ ID NO:106)

Toxin Sequence:
Ala-Thr-Asp-Cys-Ile-Xaa1-Ala-Gly-Asn-Xaa5-Cys-Gly-Xaa3-Thr-Val-Met-Lys-Ile-Cys-Cys-Gly-Phe-Cys-Ser-Xaa3-Xaa5-Ser-Lys-Ile-Cys-Met-Asn-Xaa5-Xaa3-Gln-Asn-^ (SEQ ID NO:107)

Name: Cn6.4
Species: consors
Cloned: Yes

DNA Sequence:
ATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCTCCTGACGGCCTGTCAACTC
CTCACAGCTGATGACTCCAGAGGTACGCAGAAGCATCGTGCCCTGAGGTCGGACAC
CAAACTCTCCATGTCGACTCGCTGCAAAGGTAAAGGAGCATCATGTACAAGGCTTA
TGTATGACTGCTGCCACGGTTCTTGCAGCAGCAGCAAGGGTAGATGTGGCTGATCC
GGCGCCTGATCTTCCCCCTTCTGTGCTCTATCCTTTTCTGCCTGAGTCCTCCTTACCT
GAGAGGTGGTCATGAACCACTCATCACCTGCTCCCCTG (SEQ ID NO:108)

Translation:
MKLTCVVIVAVLLLTACQLLTADDSRGTQKHRALRSDTKLSMSTRCKGKGASCTRLM
YDCCHGSCSSSKGRCG (SEQ ID NO:19)

Toxin Sequence:
Cys-Lys-Gly-Lys-Gly-Ala-Ser-Cys-Thr-Arg-Leu-Met-Xaa5-Asp-Cys-Cys-His-Gly-Ser-Cys-Ser-Ser-Ser-Lys-Gly-Arg-Cys-# (SEQ ID NO:110)

Name: Cn6.5
Species: consors
Cloned: Yes

DNA Sequence:
GGATCCATGAAACTGACGTGCATGGTGATCGTCGCCGTGCTGCTCCTGACGGCCTGT
CAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATCGTGCCCTGAGGTC
GGACACCAAACTCTCCATGTCAACTCGCTGCAAGGGTAAAGGAGCATCATGTCATA
GGACTTCGTATGACTGCTGCACCGGTTCTTGCAACAGAGGTAAATGTGGCTGATCCG
GCGCCTGATCTTCCCCCTTCTGTGCTCTATCCTTTTCTGCCTGAGTCATCCATACCTG
TGCTCGAG (SEQ ID NO:111)

Translation:
MKLTCMVIVAVLLLTACQLITADDSRGTQKHRALRSDTKLSMSTRCKGKGASCHRTSY
DCCTGSCNRGKCG (SEQ ID NO:112)

Toxin Sequence:
Cys-Lys-Gly-Lys-Gly-Ala-Ser-Cys-His-Arg-Thr-Ser-Xaa5-Asp-Cys-Cys-Thr-Gly-Ser-Cys-Asn-Arg-Gly-Lys-Cys-# (SEQ ID NO:113)

Name: Cn6.6
Species: consors
Cloned: Yes

DNA Sequence:
GGATCCATGAAACTGACGTGCGTGGTGATCGTCGCCGTGCTGCTCCTGACGGCCTGT
CAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATCGTGCCCTGAAGTC
GGACACCAAACTCTCCATGTTAACTTTGCGCTGCGCATCTTACGGAAAACCTTGTGG

TATTTACAACGACTGCTGCAATACATGCGATCCAGCCAGAAAGACATGTACGTAGC
TGATCCGGCGTCTGATCTTCCCCCTTCTGTGCTCTATCCTTTTCTGCCTGAGTCATCC
ATACCTGTGCTCGAG (SEQ ID NO:114)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQKHRALKSDTKLSMLTLRCASYGKPCGIYN
DCCNTCDPARKTCT (SEQ ID NO:115)

Toxin Sequence:
Cys-Ala-Ser-Xaa5-Gly-Lys-Xaa3-Cys-Gly-Ile-Xaa5-Asn-Asp-Cys-Cys-Asn-Thr-Cys-Asp-
Xaa3-Ala-Arg-Lys-Thr-Cys-Thr-^ (SEQ ID NO:116)

Name: Cn6.7
Species: consors
Cloned: Yes

DNA Sequence:
GGATCCATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCTCCTGACGGCCTGT
CAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATCGTGCCCTGAGGTC
GGACACCAAACTCTCCATGTCGACTCGCTGCAAGGGTACAGGAAAACCATGCAGTA
GGGTTGCGTATAACTGCTGCACCGGTTCTTGCAGATCAGGTAAATGTGGCTGATCCA
GTGCCTGATCTTCCCCCTTCTGTGCTCTATCCTTTTCTGCCTGAGTCCTCCTTACCTG
AGAGTGGTCATGAACCACTCATCACCTGCTCCTCTGGAGGCTTCAGAGGAGCTACAT
TGAAATAAAAGCCGCATTGCANTGNANAAAANNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNGGAAAAAAAAAAAAAAAAAAA (SEQ ID NO:117)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQKHRALRSDTKLSMSTRCKGTGKPCSRVAY
NCCTGSCRSGKCG (SEQ ID NO:118)

Toxin Sequence:
Cys-Lys-Gly-Thr-Gly-Lys-Xaa3-Cys-Ser-Arg-Val-Ala-Xaa5-Asn-Cys-Cys-Thr-Gly-Ser-Cys-
Arg-Ser-Gly-Lys-Cys-# (SEQ ID NO:119)

Name: Cn6.8
Species: consors
Cloned: Yes

DNA Sequence:
GGATCCATGAAACTGACGTGCATGGTGATCGTCGCCGTGCTGCTCCTGACGGCCTGT
CAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATCGTTCCCTGAGGTC
GACCACCAAAGTCTCCAAGTCGACTAGCTGCATGAAAGCCGGGTCTTATTGCCGCTC
TACTACGAGAACCTGCTGCGGTTATTGCGCTTATTTCGGCAAATTTTGTATTGACTTT
CCCAGCAACTGATCTTCCCCCTACTGTGCTCTATCCTTTTCTGCCTCTGCCTGAGTCC
TCCTTACCTGAGAGTGGTCATGAACCACTCATCACCTGCTCCCCCTGGAGGCCTCAGA

GGAGCTACAATGAAATAAAAGCCGCATTGCAAAAAAAAAAAAAAAAAAAAAA (SEQ ID NO:120)

Translation:

MKLTCMVIVAVLLLTACQLITADDSRGTQKHRSLRSTTKVSKSTSCMKAGSYCRSTTRT CCGYCAYFGKFCIDFPSN (SEQ ID NO:121)

Toxin Sequence:

Ser-Thr-Ser-Cys-Met-Lys-Ala-Gly-Ser-Xaa5-Cys-Arg-Ser-Thr-Thr-Arg-Thr-Cys-Cys-Gly-Xaa5-Cys-Ala-Xaa5-Phe-Gly-Lys-Phe-Cys-Ile-Asp-Phe-Xaa3-Ser-Asn-^ (SEQ ID NO:122)

Name: Da6.8
Species: dalli
Cloned: Yes

DNA Sequence:

ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGTTC CTGACGGCCTGTCAACTCATCACAGCTGATGACTCCAGAAGTACGCAGAAGCATCG TGCTCTGAGGTCGACCATCAAACACTCCATGTTGACTAGGAGCTGCACGCCTCCCGG AGGACCTTGTGGTTATTATAATGACTGCTGCAGTCATCAATGCAATATAAGCAGAA ATAAATGCGAGTAGCTGATCCGGCATCTGATCTTCCCCTTCTGTGCTCGTCCTAACC TGAGAGTGGTCATGAACCATCATCACCTACTCCTCTGGAGGCTTCAGAGGAGCTAC ATGGAAATAAAAGCCGCATTGC (SEQ ID NO:123)

Translation:

MKLTCVVIVAVLFLTACQLITADDSRSTQKHRALRSTIKHSMLTRSCTPPGGPCGYYND CCSHQCNISRNKCE (SEQ ID NO:124)

Toxin Sequence:

Ser-Cys-Thr-Xaa3-Xaa3-Gly-Gly-Xaa3-Cys-Gly-Xaa5-Xaa5-Asn-Asp-Cys-Cys-Ser-His-Gln-Cys-Asn-Ile-Ser-Arg-Asn-Lys-Cys-Xaa1-^ (SEQ ID NO:125)

Name: Di6.1
Species: distans
Cloned: Yes

DNA Sequence:

ACCAAAACCATCATCAAAATGAAACTGACGTGCGTGTTGATCATCGCCGTGCTGTTC CTGACGGCCTGTCAACTCACTAGAGGAAAGCTGGAGCGTCCTGTTCTGAGGTCGAG CGACCAAACCTCCGGGTCAACGAAGAGATGCGAAGATCCTGGTGAACCTTGCGGAA GTGATCATTCCTGCTGCGGCGGTAGTTGCAACCACAACGTCTGCGCCTGAAGCTGGT CTGGCATCTGACCATTCCCCTTCTGTACTCTATCTCTATTGCCTGAGTCATCTTTACC TGTGAGTGGTCATGAATCTCTCAATACCTTCTCCCCTGGAGGCTTCAGAAGAACTAG ATTGAAATA (SEQ ID NO:126)

Translation:
MKLTCVLIIAVLFLTACQLTRGKLERPVLRSSDQTSGSTKRCEDPGEPCGSDHSCCGGSC
NHNVCA (SEQ ID NO:127)

Toxin Sequence:
Cys-Xaa1-Asp-Xaa3-Gly-Xaa1-Xaa3-Cys-Gly-Ser-Asp-His-Ser-Cys-Cys-Gly-Gly-Ser-Cys-
Asn-His-Asn-Val-Cys-Ala-^ (SEQ ID NO:128)

Name: E6.2
Species: ermineus
Cloned: Yes

DNA Sequence:
ATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCTCCTGACGGCCTGTCAACTC
ATCACAGCTGACGACTCCAGACGTACGCAGAAGCATCGTGCCCTGAGGTCGACCAC
CAAACGCGCCACGTCGAATCGCCCCTGCAAGCCGAAAGGACGAAAATGTTTTCCGC
ATCAGAAGGACTGCTGCAATAAAACGTGCACCAGATCAAAATGTCCCTGATCTTCC
CCCTTCTGTGCTGTATCCTTTTCTGCCTGAGTCCTCCTTACCTGAGAGTGGTCAGTAA
CCACTCATCACCATCTCCTCTGGAGG (SEQ ID NO:129)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRRTQKHRALRSTTKRATSNRPCKPKGRKCFPHQK
DCCNKTCTRSKCP (SEQ ID NO:130)

Toxin Sequence:
Xaa3-Cys-Lys-Xaa3-Lys-Gly-Arg-Lys-Cys-Phe-Xaa3-His-Gln-Lys-Asp-Cys-Cys-Asn-Lys-Thr-
Cys-Thr-Arg-Ser-Lys-Cys-Xaa3-^ (SEQ ID NO:131)

Name: E6.3
Species: ermineus
Cloned: Yes

DNA Sequence:
AACTCATCACAGCTGATGACTCCAGAGGTACGCAGAACGATCGTGCCCTGAGGTCG
ACCACCAAACTCTCCATGCTGACTCGGGCCTGCTGGTCTTCCGGAACACCTTGTGGT
ACTGATAGTTTATGCTGCGGTGGATGCAATGTATCCAAAAGTAAATGTAACTAGCTG
ATTCGGCGTCTGAACTTCCCCCTTCTGTGCTCTATCCTTTTCTGCCCGAGTCCTCCAT
ACCTGAGAATGGTCATGAACCACTCATCACCTACTCCTCTGGAGACCTCAGAAGAG
CTACACTGAAATAAAAGCGCTTGC (SEQ ID NO:132)

Translation:
LITADDSRGTQNDRALRSTTKLSMLTRACWSSGTPCGTDSLCCGGCNVSKSKCN (SEQ
ID NO:133)

Toxin Sequence:

Ala-Cys-Xaa4-Ser-Ser-Gly-Thr-Xaa3-Cys-Gly-Thr-Asp-Ser-Leu-Cys-Cys-Gly-Gly-Cys-Asn-Val-Ser-Lys-Ser-Lys-Cys-Asn-^ (SEQ ID NO:134)

Name: G6.1
Species: geographus
Cloned: Yes

DNA Sequence:
GGATCCATGAAACTGACGTGCGTGGTGATCGTCGCCGTGCTGCTCCTGACGGCCTGT
CAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATCGTGCCCTGGGGTC
GACCACCGAACTCTCCTTGTCGACTCGCTGCAAGTCACCCGGATCTTCATGTTCACC
GACTAGTTATAATTGCTGCAGGTCTTGCAATCCATACGCCAAAAGATGTTACGGCTA
ATCCAGCGCCTGATCTTCCCCCTTCTGTGCTCTATCCCTTCCTGTCTGAGTCCTCCTT
ACCTGAGAGTGGTCATGAACCACTCCTCACCTACTTCTCTGGAGGCTTCGGAGGAGC
TACATTGAAATAAAAGCCGCATTGTAAAAAAAAAAAAAAAAAAA (SEQ ID NO:135)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQKHRALGSTTELSLSTRCKSPGSSCSPTSYNC
CRSCNPYAKRCYG (SEQ ID NO:136)

Toxin Sequence:
Cys-Lys-Ser-Xaa3-Gly-Ser-Ser-Cys-Ser-Xaa3-Thr-Ser-Xaa5-Asn-Cys-Cys-Arg-Ser-Cys-Asn-Xaa3-Xaa5-Ala-Lys-Arg-Cys-Xaa5-# (SEQ ID NO:137)

Name: G6.2
Species: geographus
Cloned: Yes

DNA Sequence:
GGATCCATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCTCCTGACGGCCTGT
CAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATCGTGCCCTGAGGTC
GTCCACCAAACTCACCTTGTCGACTCGCTGCAAATCACCCGGAACTCCATGTTCAAG
GGGTATGCGTGATTGCTGCACGCCTTGCTTGTTATACAGCAACAAATGTAGGCGCTA
CTAACCCAGCGCCTGATCTTCCCCCTTCTGTGCTCTATTCCTTTCTGCCTGAGTCCTC
CTTACCTGAAAGTGGTCATGAACCACTCATCACCTACTTCTCTGGAGGCTTCAGAAG
AGCTACATTGAAATAAAAGCCGCATTGCAATGACAAAAAAAAAAAAAAAAAAAAA
(SEQ ID NO:138)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQKHRALRSSTKLTLSTRCKSPGTPCSRGMRD
CCTPCLLYSNKCRRY (SEQ ID NO:139)

Toxin Sequence:
Cys-Lys-Ser-Xaa3-Gly-Thr-Xaa3-Cys-Ser-Arg-Gly-Met-Arg-Asp-Cys-Cys-Thr-Xaa3-Cys-Leu-Leu-Xaa5-Ser-Asn-Lys-Cys-Arg-Arg-Xaa5-^ (SEQ ID NO:140)

Name: w-GVIA
Species: geographus
Cloned: Yes

DNA Sequence:
GGAATTCCGTTTCTGCGCTGCTTCCTTTGGCATCACCAAAACCATCATCAAAATGAA
ACTGACGTGTGTGGTGATCGTCGCCGTGCTGCTCCTGACGGCCTGTCAACTCATCAC
AGCTGATGACTCCAGAGGTACGCAGAAGCATCGTGCCCTGGGGTCGACCACCGAAC
TCTCCTTGTCGACTCGCTGCAAGTCACCCGGATCTTCATGTTCACCGACTAGTTATA
ATTGCTGCAGGTCTTGCAATCCATACACCAAAAGATGTTACGGCTAATCCAGCGCCT
GATCTTCCCTGCTCTGAGTCCTCCTTACCTGAGAGTGGTCATGAACCACTCATCACC
TACTTCTCTAGGCGGTTCGGAGGAGCTACATTGAAATAAAAGCCGCATTGCAAAAA
AAAAAAAAAA (SEQ ID NO:141)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQKHRALGSTTELSLSTRCKSPGSSCSPTSYNC
CRSCNPYTKRCYG (SEQ ID NO:142)

Toxin Sequence:
Cys-Lys-Ser-Xaa3-Gly-Ser-Ser-Cys-Ser-Xaa3-Thr-Ser-Xaa5-Asn-Cys-Cys-Arg-Ser-Cys-Asn-Xaa3-Xaa5-Thr-Lys-Arg-Cys-Xaa5-# (SEQ ID NO:143)

Name: w-GVIB
Species: geographus
Isolated: Yes

Toxin Sequence:
Cys-Lys-Ser-Xaa3-Gly-Ser-Ser-Cys-Ser-Xaa3-Thr-Ser-Xaa5-Asn-Cys-Cys-Arg-Ser-Cys-Asn-Xaa3-Xaa5-Thr-Lys-Arg-Cys-Xaa5-Gly-# (SEQ ID NO:144)

Name: w-GVIC
Species: geographus
Isolated: Yes

Toxin Sequence:
Cys-Lys-Ser-Xaa3-Gly-Ser-Ser-Cys-Ser-Xaa3-Thr-Ser-Xaa5-Asn-Cys-Cys-Arg-Ser-Cys-Asn-Xaa3-Xaa5-Thr-Lys-Arg-Cys-# (SEQ ID NO:145)

Name: w-GVIIA
Species: geographus
Isolated: Yes
Cloned: Yes

DNA Sequence:
CATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATCGTGCCCTGAGGTCGTCCA
CCAAACTCACCTTGTCGACTCGCTGCAAATCACCCGGAACTCCATGTTCAAGGGGTA
TGCGTGATTGCTGCACGTCTTGCTTGTTATACAGCAACAAATGTAGGCGCTACTAAC
CCAGCGCCTGATCTTCCCCCTTCTGTGCTCTATTCCTTTCTGCCTGAGTCCTCCTTAC
CTGAAAGTGGTCATGAACCACTCATCACCTACTTCTCTGGAGGCTTCAGAAGAGCTA
CATTGAAATAAAAGCCGCATTGCAATGAC (SEQ ID NO:146)

Translation:
ITADDSRGTQKHRALRSSTKLTLSTRCKSPGTPCSRGMRDCCTSCLLYSNKCRRY (SEQ ID NO:147)

Toxin Sequence:
Cys-Lys-Ser-Xaa3-Gly-Thr-Xaa3-Cys-Ser-Arg-Gly-Met-Arg-Asp-Cys-Cys-Thr-Ser-Cys-Leu-Leu-Xaa5-Ser-Asn-Lys-Cys-Arg-Arg-Xaa5-# (SEQ ID NO:148)

Name: w-GVIIB
Species: geographus
Isolated: Yes

Toxin Sequence:
Cys-Lys-Ser-Xaa3-Gly-Thr-Xaa3-Cys-Ser-Arg-Gly-Met-Arg-Asp-Cys-Cys-Thr-Ser-Cys-Leu-Ser-Xaa5-Ser-Asn-Lys-Cys-Arg-Arg-Xaa5-# (SEQ ID NO:149)

Name: La6.1
Species: laterculatus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAACTCATCACCGCTGATGACTCCAGAGGTACGCAGAAGCATC
GTGCCCTGAGGTCGACCACCAATCTCTCCATGCTGACTCGGAAGTGCTGGCCTTCCG
GAAGCTATTGTCGTGCGAATAGTAAATGCTGCAGTGGATGCGATCGGAACAGAAAT
AAATGTTACTAGCTGATTCGGCGTCTGAACTTCCTCCTTCTGTGCTCTATCCTTTTCT
GCCCGAGTCCTCCATACCTGAGAGTGGTCATGAACCACTCAACTCCTACTCCTCTGG
AGGCCTCAGAAGAGCTACATTGAAATAAAAGCCGCATTGC (SEQ ID NO:150)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQKHRALRSTTNLSMLTRKCWPSGSYCRANS
KCCSGCDRNRNKCY (SEQ ID NO:151)

Toxin Sequence:
Lys-Cys-Xaa4-Xaa3-Ser-Gly-Ser-Xaa5-Cys-Arg-Ala-Asn-Ser-Lys-Cys-Cys-Ser-Gly-Cys-Asp-Arg-Asn-Arg-Asn-Lys-Cys-Xaa5-^ (SEQ ID NO:152)

Name: La6.2
Species: laterculatus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATC
GTGCCCTGAGGTCGACCACCAAACTCTCCATATCGACTCGCTGCCTTCCTCCCGGAT
CATATTGTAAGGCGACAACGGAAGTCTGCTGCTCTTCTTGCCTTCAATTCGCTCAGA
TATGTTCGGGTTGATCTTCCCTCTTCTGTGCTCTATCCTTTTCTGCCTGAGTCCTCCAT
ACCTGAGAATGGTCATGAACCACTCAACATCTACTCCTCTGGAGGCCTCAGAAGAG
CTATATTGAAATAAAAGCCGCATTGC (SEQ ID NO:153)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQKHRALRSTTKLSISTRCLPPGSYCKATTEVC
CSSCLQFAQICSG (SEQ ID NO:154)

Toxin Sequence:
Cys-Leu-Xaa3-Xaa3-Gly-Ser-Xaa5-Cys-Lys-Ala-Thr-Thr-Xaa1-Val-Cys-Cys-Ser-Ser-Cys-Leu-Gln-Phe-Ala-Gln-Ile-Cys-Ser-# (SEQ ID NO:155)

Name: La6.3
Species: laterculatus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATC
GTGCCCTGAGGTCGACCACCAATCTCTCCATGTCGACTCGCTGCAAGTCTCCCGGAT
CATCATGTAGCGTGTCTATGCGTAACTGCTGCACTTCTTGCAATTCACGCACCAAGA
AATGTACGCGACGTGGCTGAACTTCCCCCTTCTGTGCTCTATCCTTTTCTGCCCGAGT
CCTCCATACCTGAGAGTGGTCATGAACCACTCAACATCTACTCCTCTGGAGGCCTCA
GAAGAGCTATATTGAAATAAAAGCCGCATTGC (SEQ ID NO:156)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQKHRALRSTTNLSMSTRCKSPGSSCSVSMRN
CCTSCNSRTKKCTRRG (SEQ ID NO:157)

Toxin Sequence:
Cys-Lys-Ser-Xaa3-Gly-Ser-Ser-Cys-Ser-Val-Ser-Met-Arg-Asn-Cys-Cys-Thr-Ser-Cys-Asn-Ser-Arg-Thr-Lys-Lys-Cys-Thr-Arg-Arg-# (SEQ ID NO:158)

Name: La6.4
Species: laterculatus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATC
GTGCCCTGAGGTCGACAACCAAACTCTCCATGCTGACTCGGACCTGCTGGCCTTCCG
GAACAGCTTGTGGTATTGATAGTAACTGCTGCAGTGGATGCAATGTATCCAGAAGT
AAATGTAACTAGCTGATTCGGCGTCTAAACTTCCTCCTTCTGCCTGAGTCCTCCATA
CCTGAGAGTGGTCATGAACCACATCATCACCTCATCTCTGGAGGCCTC (SEQ ID NO:159)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQKHRALRSTTKLSMLTRTCWPSGTACGIDSN
CCSGCNVSRSKCN (SEQ ID NO:160)

Toxin Sequence:
Thr-Cys-Xaa4-Xaa3-Ser-Gly-Thr-Ala-Cys-Gly-Ile-Asp-Ser-Asn-Cys-Cys-Ser-Gly-Cys-Asn-
Val-Ser-Arg-Ser-Lys-Cys-Asn-^ (SEQ ID NO:161)

Name: La6.5
Species: laterculatus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATC
GTGCCCTGAGGTCGACCACCAATCTCTCCATGCTGACTCGGAAGTGCTGGCCTTCCG
GAAGCTATTGTCGTGCGAATAGTAAATGCTGCAGTGGATGCGATCGGAACAGAAGT
AAATGTAACTAGCTGATTCGGCGTCTAAACTTCCTCCTTCTGCCTGAGTCCTCCATA
CCTGAGAGTGGTCATGAACCACTCATCACCTACTCCTCTGGAGGCCTCAAAGGAGCT
ACATTGAAATAAAAGCCGCATTGC (SEQ ID NO:162)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQKHRALRSTTNLSMLTRKCWPSGSYCRANS
KCCSGCDRNRSKCN (SEQ ID NO:163)

Toxin Sequence:
Lys-Cys-Xaa4-Xaa3-Ser-Gly-Ser-Xaa5-Cys-Arg-Ala-Asn-Ser-Lys-Cys-Cys-Ser-Gly-Cys-Asp-
Arg-Asn-Arg-Ser-Lys-Cys-Asn-^ (SEQ ID NO:164)

Name: Lp6.1
Species: leopardus
Cloned: Yes

DNA Sequence:
ATGAAACTGACGTGTGTGGTGATCGTAGCTGTGCTGTTCCTGACGGCCTGTCAACTC
ACTACAGCTGACATCTCCAGAGGTACGCGGAAGCGTCGTGCTCTGAGGTCGACCAC
CAAACTCTCCAGGTCGCTCTTTGAGTGCGCGCCTTCCGGTGGACGTTGTGGTTTTTTA
AAGTCCTGCTGCGAAGGATATTGCGATGGGGAAAGCACTTCATGTGTGAGTGGCCC
ATACAGCATCTGATCTTCCCGCCTTCAGTGCTCTATCCTTTTCTGCCTGAGTCCTCCA
TACCTCTGAGCGGTCATGAACCACTCAACACCTACTCCTCTGGAGGCTTCAGGGAAC
TATATTAAAATAAAGCCGCATTGCAACGAAANAAAAAAAAAAAAAAAAAA (SEQ ID NO:165)

Translation:
MKLTCVVIVAVLFLTACQLTTADISRGTRKRRALRSTTKLSRSLFECAPSGGRCGFLKSC
CEGYCDGESTSCVSGPYSI (SEQ ID NO:166)

Toxin Sequence:
Ser-Leu-Phe-Xaa1-Cys-Ala-Xaa3-Ser-Gly-Gly-Arg-Cys-Gly-Phe-Leu-Lys-Ser-Cys-Cys-Xaa1-Gly-Xaa5-Cys-Asp-Gly-Xaa1-Ser-Thr-Ser-Cys-Val-Ser-Gly-Xaa3-Xaa5-Ser-Ile-^ (SEQ ID NO:167)

Name: Lp6.2
Species: leopardus
Cloned: Yes

DNA Sequence:
ATGAAACTGACGTGTGTGGTGATCGTCGCTGTGCTGTTCCTGACGGCCTGTCAACTC
ACTACAGCTGACATCTCCAGAGGTACGTGGAAGCATCGTGGTGTGGGGTCGACCAC
CGGACTCTCCCCGTGGCCCTTGGACTGCACGGCTCCCAGTCAACCTTGTGGTTATTT
TCCTAGGTGCTGTGGACATTGCGATGTACGCAGGGTATGTACGAGTGGCTGATCCG
GCGTCTGATCTTTCCGCCTTCTGTGCTGTATCCTTTTCTGCCTGAGTCCTCCATACCC
GTGAGTGGTCATGAACCACTCAACACCTACTCCTCTGGAGGCTTCAGAGGAACTAT
ATTAAAATAAAGCCGCATTGCAATG (SEQ ID NO:168)

Translation:
MKLTCVVIVAVLFLTACQLTTADISRGTWKHRGVGSTTGLSPWPLDCTAPSQPCGYFPR
CCGHCDVRRVCTSG (SEQ ID NO:169)

Toxin Sequence:
Xaa4-Xaa3-Leu-Asp-Cys-Thr-Ala-Xaa3-Ser-Gln-Xaa3-Cys-Gly-Xaa5-Phe-Xaa3-Arg-Cys-Cys-Gly-His-Cys-Asp-Val-Arg-Arg-Val-Cys-Thr-Ser-# (SEQ ID NO:170)

Name: Lp6.3
Species: leopardus
Cloned: Yes

DNA Sequence:
ATGAAACTGACGTGTGTGGTGATCGTCGCTGTGCTGTTCCTGACGGCCTGTCAACTC
ACTACAGCTGACATCTCCAGAGGTACGCGGAAGCATCGTGCTCTGAGGTCGACCAC
CAAACTCTCCAGGTCGCCCTCTAGGTGCATGTCTCCCGGTGGAATTTGTGGTGATTT
TGGTGACTGCTGCGAAATTTGCAATGTGTACGGTATATGTGTGAGTGACTTACCCGG
CATCTGATCTTTCCGCCTTCTGTGCTCTATCCTTTTCTGCCTGAGTCCTCCATACCCCT
GAGTGGTCATGGACCACTCAACACCTACTCCTCTGGAGGCTTCAGAGGAACTACATT
AAAATAAAGCCGCATTGCAAAAAAAAAAAAAAAAAAAA (SEQ ID NO:171)

Translation:
MKLTCVVIVAVLFLTACQLTTADISRGTRKHRALRSTTKLSRSPSRCMSPGGICGDFGDC
CEICNVYGICVSDLPGI (SEQ ID NO:172)

Toxin Sequence:
Cys-Met-Ser-Xaa3-Gly-Gly-Ile-Cys-Gly-Asp-Phe-Gly-Asp-Cys-Cys-Xaa1-Ile-Cys-Asn-Val-Xaa5-Gly-Ile-Cys-Val-Ser-Asp-Leu-Xaa3-Gly-Ile-^ (SEQ ID NO:173)

Name: Lp6.4
Species: leopardus
Cloned: Yes

DNA Sequence:
ATGAAACTGACGTGTGTGGTGATCGTCGCTGTGCTGTTCCTGACGGCCTGTCAACTC
ACTACAGCTGATGATTCCAGAGGTACACGGAAGCATCGTGCTCTGAGGTCAACCAC
CAAACTCTCCAGGTGGCCCAGGTACTGCGCGCCTCCCGGTGGAGCTTGTGGGTTTTT
TGATCACTGCTGCGGATATTGCGAAACGTTTTACAATACGTGTAGATGAGTTGGCTG
ATCCGGCGCTTGATCTTTCCGCCTTCTGTTGCTCTATCTTTTTCTGCCTGAGTCCTCCC
ATACCCCGTTGAGTGGTCCATGAACCACTCCAACACCTACTCCCTCCTTGGAAGCTT
CCAAAGGAAACGACATTTAAAATAAATTCCCCATTGCAATTGGAAAAAAAAAAAAAA
AAAAA (SEQ ID NO:174)

Translation:
MKLTCVVIVAVLFLTACQLTTADDSRGTRKHRALRSTTKLSRWPRYCAPPGGACGFFD
HCCGYCETFYNTCR (SEQ ID NO:175)

Toxin Sequence:
Xaa5-Cys-Ala-Xaa3-Xaa3-Gly-Gly-Ala-Cys-Gly-Phe-Phe-Asp-His-Cys-Cys-Gly-Xaa5-Cys-Xaa1-Thr-Phe-Xaa5-Asn-Thr-Cys-Arg-^ (SEQ ID NO:176)

Name: L6.1
Species: lynceus
Cloned: Yes

DNA Sequence:
ATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCTCCTGACGGCCTGTCAACTC

ATCACAGCTGATGACTCCAGACGTACACAGAAGCATCGTGCCCTGAGGTCGACCAC
CAATCTCTCCATGTCGACTCGCTGCAAGTCTCCCGGATCACCATGTAGTGTGACATC
GTATAACTGCTGCACTTTTTGCTCTTCATACACTAAGAAATGTCGGGCCTCTTTATGA
ACCACTCATCACCTACTCCTCTGGAGGCCTCAGAAGAGCTACACTGAAATAAAAGC
CGCATTGG (SEQ ID NO:177)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRRTQKHRALRSTTNLSMSTRCKSPGSPCSVTSYN
CCTFCSSYTKKCRASL (SEQ ID NO:178)

Toxin Sequence:
Cys-Lys-Ser-Xaa3-Gly-Ser-Xaa3-Cys-Ser-Val-Thr-Ser-Xaa5-Asn-Cys-Cys-Thr-Phe-Cys-Ser-
Ser-Xaa5-Thr-Lys-Lys-Cys-Arg-Ala-Ser-Leu-^ (SEQ ID NO:179)

Name: L6.2
Species: lynceus
Cloned: Yes

DNA Sequence:
ATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCTCCTGACGGCCTGTCAACTC
ATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATCGTGCCCTGAGGTCGACCAC
CAAACTATCCATGTATACTCGCTGCGCAGGTCCAGGAGCAATTTGTCCTAATAGGGT
ATGCTGCGGTTATTGCAGTAAAAGAACACATCTATGTCATTCGCGAACTGGCTGATC
TTCCCCCTTCTGTGCTCTATCCTTTTTCTGCCTGAGTCCTCCATACCTGAGAATGGTC
ATGAACCACTCATCACCTACTCCTCTTGGAGACCTCAGAGGAGCTACACTGAAATA
AAAGCCGCATTGGC (SEQ ID NO:180)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQKHRALRSTTKLSMYTRCAGPGAICPNRVCC
GYCSKRTHLCHSRTG (SEQ ID NO:181)

Toxin Sequence:
Cys-Ala-Gly-Xaa3-Gly-Ala-Ile-Cys-Xaa3-Asn-Arg-Val-Cys-Cys-Gly-Xaa5-Cys-Ser-Lys-Arg-
Thr-His-Leu-Cys-His-Ser-Arg-Thr-# (SEQ ID NO:182)

Name: L6.3
Species: lynceus
Cloned: Yes

DNA Sequence:
ATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCTGCTAGCGGCCTGTCAACTA
CTACACGCTGATGACTCCAGAGGTACGCAGAAGACTGCTGCCCGAGGTCGACCACC
AAAACTCTCCATGCTGACTCGGGCCTGCTGGTCTTCCGGAACACCTTGTGGTACTGA
TAGTTTATGCTGCGGTGGATGCAATGTATCCAAAAGTAAATGTAACTAGCTGATTCG
GCGTCTGAACTTCCCCCTTCTGTGCTCTATCCTTTTCTGCCCGAGTCCTCCATACCTG

AGAATGGTCATGAACCACTCATCACCTACTCCTCTGGAGACCTCAGAAGAGCTACA
CTGAAATAAAAGCGCATTGC (SEQ ID NO:183)

Translation:

MKLTCVVIVAVLLLAACQLLHADDSRGTQKTAARGRPPKLSMLTRACWSSGTPCGTDS
LCCGGCNVSKSKCN (SEQ ID NO:184)

Toxin Sequence:

Ala-Cys-Xaa4-Ser-Ser-Gly-Thr-Xaa3-Cys-Gly-Thr-Asp-Ser-Leu-Cys-Cys-Gly-Gly-Cys-Asn-
Val-Ser-Lys-Ser-Lys-Cys-Asn-^ (SEQ ID NO:185)

Name: L6.4
Species: lynceus
Cloned: Yes

DNA Sequence:

ATGAAACTGACGTGTGTGGTGATCGTCGCCGAGCTACTCCTAACGGCCTGTCAACTC
ATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATCGTGCCCTGAGGTCGACCAC
CAATCTCTCCATGCTGACTCGGAAGTGCTGGTCTCCCGGAACCTATTGTCGTGCGCA
TAGTAAATGCTGCCGTGGATGCGATCAGAACAGAAATAAATGTTACTAGCTGATTC
GGCGTCTGAACTTCCTCCTTCTGTGCTCTATCCTTTTTCTGCCTGAGTCCTCCATACC
TGAGAATGGTCATGAACCACTCATCACCTACTCCTCTGGAGGCCTCAGAGGAGCCT
ACACTGAAATAAAAGCCGCATTGG (SEQ ID NO:186)

Translation:

MKLTCVVIVAELLLTACQLITADDSRGTQKHRALRSTTNLSMLTRKCWSPGTYCRAHS
KCCRGCDQNRNKCY (SEQ ID NO:187)

Toxin Sequence:

Lys-Cys-Xaa4-Ser-Xaa3-Gly-Thr-Xaa5-Cys-Arg-Ala-His-Ser-Lys-Cys-Cys-Arg-Gly-Cys-Asp-
Gln-Asn-Arg-Asn-Lys-Cys-Xaa5-^ (SEQ ID NO:188)

Name: M6.1
Species: magus
Cloned: Yes

DNA Sequence:

ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATC
GTGCCCTGAGGTCGGACACCAAACTCTCCATGTCGACTCGCTGCAAGGGTACAGGA
AAACCATGCAGTAGGATTGCGTATAACTGCTGCACCGGTTCTTGCAGATCAGGTAA
ATGTGGCTGATCCAGTGCCTGATCTTCCCCCTTCTGTGCTCTATCCTTTTTCTGCCTG
AGTCCTCCTTACCTGAGAGTGGTCATGAACCACTCA (SEQ ID NO:189)

Translation:

MKLTCVVIVAVLLLTACQLITADDSRGTQKHRALRSDTKLSMSTRCKGTGKPCSRIAYN CCTGSCRSGKCG (SEQ ID NO:190)

Toxin Sequence:

Cys-Lys-Gly-Thr-Gly-Lys-Xaa3-Cys-Ser-Arg-Ile-Ala-Xaa5-Asn-Cys-Cys-Thr-Gly-Ser-Cys-Arg-Ser-Gly-Lys-Cys-# (SEQ ID NO:191)

Name: M6.2
Species: magus
Cloned: Yes

DNA Sequence:

ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATC
GTGCCCTGAAGTCGGACACCAAACTCTCCATGTTAACTTTGCGCTGCGCATCTTACG
GAAAACCTTGTGGTATTTACAACGACTGCTGCAATACATGCGATCCAGCCAGAAAG
ACATGTACGTAGCTGATCCGGCGTCTGATCTTCC (SEQ ID NO:192)

Translation:

MKLTCVVIVAVLLLTACQLITADDSRGTQKHRALKSDTKLSMLTLRCASYGKPCGIYN DCCNTCDPARKTCT (SEQ ID NO:193)

Toxin Sequence:

Cys-Ala-Ser-Xaa5-Gly-Lys-Xaa3-Cys-Gly-Ile-Xaa5-Asn-Asp-Cys-Cys-Asn-Thr-Cys-Asp-Xaa3-Ala-Arg-Lys-Thr-Cys-Thr-^ (SEQ ID NO:194)

Name: w-MVIIB
Species: magus
Isolated: Yes
Cloned: Yes

DNA Sequence:

GAATTTTCAGCATCACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATC
GTCGCCGTGCTGCTCCTGACGGCCTGTCAACTCATCACAGCTGATGACTCCAGAGGT
ACGCAGAAGCATCGTGCCCTGAGGTCGGACACCAAACTCTCCATGTCAACTCGCTG
CAAGGGTAAAGGAGCATCATGTCATAGGACTTCGTATGACTGCTGCACCGGTTCTTG
CAACAGAGGTAAATTTGGCTGATCCGCC (SEQ ID NO:195)

Translation:

MKLTCVVIVAVLLLTACQLITADDSRGTQKHRALRSDTKLSMSTRCKGKGASCHRTSY DCCTGSCNRGKFG (SEQ ID NO:196)

Toxin Sequence:

Cys-Lys-Gly-Lys-Gly-Ala-Ser-Cys-His-Arg-Thr-Ser-Xaa5-Asp-Cys-Cys-Thr-Gly-Ser-Cys-Asn-Arg-Gly-Lys-Cys-# (SEQ ID NO:197)

Name: Mi6.1
Species: miles
Cloned: Yes

DNA Sequence:
GGATCCATGAAACTGACGTGCGTGGTGATCATCGCCATGCTGTTCCTGACAGCCTAT
CAACTCGCTACAGCTGCGAGCTACGCCAAAGGTAAACAGAAGCATCGTGCTCTGAG
GCCAGCTGACAAACACCTCAGGTTGACCAAGCGTTGCAATGATCGCGGTGGAGGTT
GCAGTCAACATCCTCACTGCTGCGGTGGAACTTGCAATAAGCTTATTGGCGTATGTC
TGTAAAGCTGGTCTGCCGTCTGATATTCCCTTTCTGTGCTTCATCCTCTTTTGCCTGA
GTCATCCATACCTGTGAATGGTTAAGAGCCACTCAATACCTATTCCTCTGGGGGCTT
CAGAGGAACTACTTTAC (SEQ ID NO:198)

Translation:
MKLTCVVIIAMLFLTAYQLATAASYAKGKQKHRALRPADKHLRLTKRCNDRGGGCSQ
HPHCCGGTCNKLIGVCL (SEQ ID NO:199)

Toxin Sequence:
Cys-Asn-Asp-Arg-Gly-Gly-Gly-Cys-Ser-Gln-His-Xaa3-His-Cys-Cys-Gly-Gly-Thr-Cys-Asn-Lys-Leu-Ile-Gly-Val-Cys-Leu-^ (SEQ ID NO:200)

Name: Mn6.1
Species: monachus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGAGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATC
GTGCCCTGAGGTCGGACACCAAACTCTCCATATCGACTCGCTGCAAGTCTACAGGA
AAATCATGCAGTAGGATTGCGTATAACTGCTGCACCGGTTCTTGCAGATCAGGTAA
ATGTGGCTGATCCAGCGCCTGATCTTCCCCCTTCTGTGCTCTATCCTTTTCTGCCTGA
GTCCTCCTTA (SEQ ID NO:201)

Translation:
MKLTSVVIVAVLLLTACQLITADDSRGTQKHRALRSDTKLSISTRCKSTGKSCSRIAYNC
CTGSCRSGKCG (SEQ ID NO:202)

Toxin Sequence:
Cys-Lys-Ser-Thr-Gly-Lys-Ser-Cys-Ser-Arg-Ile-Ala-Xaa5-Asn-Cys-Cys-Thr-Gly-Ser-Cys-Arg-Ser-Gly-Lys-Cys-# (SEQ ID NO:203)

Name: Mn6.2
Species: monachus

Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGAGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATC
GTGCCCTGAGGTCGGACACCAACCTCTCCATGTCGACTCGCTGCAAGGGTAAAGGA
TCTTCATGTAGTAGGACCATGTATAACTGCTGCACCGGTTCTTGCAACAGAGGTAAA
TGTGGCTGATCCAGCGCCTGATCTTCCCCCTTC (SEQ ID NO:204)

Translation:
MKLTSVVIVAVLLLTACQLITADDSRGTQKHRALRSDTNLSMSTRCKGKGSSCSRTMY
NCCTGSCNRGKCG (SEQ ID NO:205)

Toxin Sequence:
Cys-Lys-Gly-Lys-Gly-Ser-Ser-Cys-Ser-Arg-Thr-Met-Xaa5-Asn-Cys-Cys-Thr-Gly-Ser-Cys-
Asn-Arg-Gly-Lys-Cys-# (SEQ ID NO:206)

Name: O6.1
Species: obscurus
Cloned: Yes

DNA Sequence:
ctctctctctctgctggacAGGTCGCCTCCCTGCATGAAAGGCGGATCGTCATGCCGCGGTAC
TACGGGAGTCTGTTGCGGTTTTTGCAGTGATTTCGGCTATAAATGTAGGGACTATCC
CCAAAACTGATCTTCCCCCTTCTGTGCTCTATCCTTTTCTGTCCGAGTCCTCCTGACC
TGAGAGTGGTCATGAACCACTCATCACCTACCCCTCTGGGGCTTCACAGGATCTACA
TTGAAATAAAAGCCGCATTGC (SEQ ID NO:207)

Translation:
LLDRSPPCMKGGSSCRGTTGVCCGFCSDFGYKCRDYPQN (SEQ ID NO:208)

Toxin Sequence:
Ser-Xaa3-Xaa3-Cys-Met-Lys-Gly-Gly-Ser-Ser-Cys-Arg-Gly-Thr-Thr-Gly-Val-Cys-Cys-Gly-
Phe-Cys-Ser-Asp-Phe-Gly-Xaa5-Lys-Cys-Arg-Asp-Xaa5-Xaa3-Gln-Asn-^ (SEQ ID NO:209)

Name: O6.2
Species: obscurus
Cloned: Yes

DNA Sequence:
ctctctctctctgctggacAGGTCGACTCGCTGCTTGCCTGACGGAACGTCTTGCCTTTTTAGT
AGGATCAGATGCTGCGGTACTTGCAGTTCAATCTTAAAGTCATGTGTGAGCTGATCC
AGCGGTTGATCTTCCTCCCTCTGTGCTCCATCCTTTTCTGCCTGAGTTCTCCTTACCT
GAGAGTGGTCATGAACCACTCATCACCTACTCTTCTGGAGGCTTCAGAGGAGCTAC
ATTGAAATAAAAGCCGCATTGC (SEQ ID NO:210)

Translation:
RSTRCLPDGTSCLFSRIRCCGTCSSILKSCVS (SEQ ID NO:211)

Toxin Sequence:
Cys-Leu-Xaa3-Asp-Gly-Thr-Ser-Cys-Leu-Phe-Ser-Arg-Ile-Arg-Cys-Cys-Gly-Thr-Cys-Ser-Ser-Ile-Leu-Lys-Ser-Cys-Val-Ser-^ (SEQ ID NO:212)

Name: Pu6.2
Species: pulicarius
Cloned: Yes

DNA Sequence:
ATGAAACTGACGTGTGTGGTGATCATCGCCGTGCTGTTCCTGACGGCCTGTCAACTC
ATTACAGCTGAGACTTACTCCAGAGGTAAGCAGAAGCACCGTGCTTTGAGGTCAAC
TGACAAAAACTCCAAGTTGACTAGGCAGTGCTCGCCTAACGGTGGATCTTGTTCTCG
TCATTTTCACTGCTGCAGCCTCTATTGCAATAAAAATACTGGCGTATGTATTGCAAC
CTAATACCCGTGTGTGGTCATGAACCACTCAATACCCTCTCCTCTGGAGGCTTCAGA
GGAACTGCATTGAAATAAAACTGCATTGCNTTGACCAAAAAAAAAAA (SEQ ID NO:213)

Translation:
MKLTCVVIIAVLFLTACQLITAETYSRGKQKHRALRSTDKNSKLTRQCSPNGGSCSRHF
HCCSLYCNKNTGVCIAT (SEQ ID NO:214)

Toxin Sequence:
Xaa2-Cys-Ser-Xaa3-Asn-Gly-Gly-Ser-Cys-Ser-Arg-His-Phe-His-Cys-Cys-Ser-Leu-Xaa5-Cys-Asn-Lys-Asn-Thr-Gly-Val-Cys-Ile-Ala-Thr-^ (SEQ ID NO:215)

Name: P6.1
Species: purpurascens
Cloned: Yes

DNA Sequence:
ATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGTTCCTGACGGCCTGTCAACTC
ATCACAGCTGATGACTCCAGACGTACGCAGAAGCATCGTGCCCTGAGGTCGACCAC
CAAAGGCGCCACGTCGAATCGCCCCTGCAAGACACCCGGACGAAAATGTTTTCCGC
ATCAGAAGGACTGCTGCGGTCGAGCGTGCATCATCACAATATGTCCCTGATCTTCCC
CCTTCTGTGCTGTATCCTTTTCTGCCTGAGTCTCCTTACCTGAGAGTGGTCATGAA
(SEQ ID NO:216)

Translation:
MKLTCVVIVAVLFLTACQLITADDSRRTQKHRALRSTTKGATSNRPCKTPGRKCFPHQK
DCCGRACIITICP (SEQ ID NO:217)

Toxin Sequence:
Xaa3-Cys-Lys-Thr-Xaa3-Gly-Arg-Lys-Cys-Phe-Xaa3-His-Gln-Lys-Asp-Cys-Cys-Gly-Arg-Ala-Cys-Ile-Ile-Thr-Ile-Cys-Xaa3-^ (SEQ ID NO:218)

Name: P6.2
Species: purpurascens
Isolated: Yes
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATC
GTGCCCTGAGGTCGACCACCAAACTCTTCACGTCGAAAAGCTGCAAGCTTCCCGGA
GCATATTGTAATGCAGAAGATTATGACTGCTGCCTTAGATGCAAAGTTGGAGGTAC
ATGTGGCTGATCCAGTGCCTGATCTTCCCCCTTCTGTGCTCTATCCTTTTCTGCCTGA
GTCCTCCTTACCTAAGAGTGGTCATGAACCACTCATCACCTTCTCCTCTGGAGGCTT
C (SEQ ID NO:219)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQKHRALRSTTKLFTSKSCKLPGAYCNAEDYD
CCLRCKVGGTCG (SEQ ID NO:220)

Toxin Sequence:
Ser-Cys-Lys-Leu-Xaa3-Gly-Ala-Xaa5-Cys-Asn-Ala-Xaa1-Asp-Xaa5-Asp-Cys-Cys-Leu-Arg-Cys-Lys-Val-Gly-Gly-Thr-Cys-# (SEQ ID NO:221)

Name: P6.3
Species: purpurascens
Cloned: Yes

DNA Sequence:
ATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGTTCCTGACGGCCTGTCAACTC
ATCACAGCTGATGACTCCAGACGTACGCAGAAGCATCGTGCCCTGAGGTCGACCAC
CAAACGCGCCACGTCGAATCGCCCCTGCAAGAAAACCGGACGAAAATGTTTTCCGC
ATCAGAAGGACTGCTGCGGTCGAGCGTGCATCATCACAATATGTCCCTGATCTTCCC
CCTTCTGTGCTGTATCCTTTTCTGCCTGAGTCCTCCTTACCTGAGAGTGGTCATGAAC
CACTCATCACCTTCTCCTCTGGAGGCTTCAGAG (SEQ ID NO:222)

Translation:
MKLTCVVIVAVLFLTACQLITADDSRRTQKHRALRSTTKRATSNRPCKKTGRKCFPHQK
DCCGRACIITICP (SEQ ID NO:223)

Toxin Sequence:
Xaa3-Cys-Lys-Lys-Thr-Gly-Arg-Lys-Cys-Phe-Xaa3-His-Gln-Lys-Asp-Cys-Cys-Gly-Arg-Ala-Cys-Ile-Ile-Thr-Ile-Cys-Xaa3-^ (SEQ ID NO:224)

Name: R6.1
Species: radiatus
Cloned: Yes

DNA Sequence:
GCTGATGCCTGATCTTCATCGTTCTTCCCTGTCTCCTTTGGCATCACCAAAACCATCA
TCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGGTCCTGACGGCCTGTC
AACTCATCACAGCTGATGACTCCAGAGGTATGCAGAAACATCATGCCCTGGGGTCG
ATCAGCAGTCTCTTTAAGTCGACCCGTCATGGCTGCAAACCCCTCAAACGTCGTTGT
TTCAATGATAAAGAATGCTGCAGCAAATTTTGCAATTCAGTCCGAAAGCAGTGTGG
ATAAATGGCTAAAAAACTGAATAAAAGCCGCATTGCAAAAAAAA (SEQ ID NO:225)

Translation:
MKLTCVVIVAVLVLTACQLITADDSRGMQKHHALGSISSLFKSTRHGCKPLKRRCFNDK
ECCSKFCNSVRKQCG (SEQ ID NO:226)

Toxin Sequence:
His-Gly-Cys-Lys-Xaa3-Leu-Lys-Arg-Arg-Cys-Phe-Asn-Asp-Lys-Xaa1-Cys-Cys-Ser-Lys-Phe-
Cys-Asn-Ser-Val-Arg-Lys-Gln-Cys-# (SEQ ID NO:227)

Name: R6.2
Species: radiatus
Cloned: Yes

DNA Sequence:
GAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGGTCCTGACGGCCTGTCA
ACTCATCACAGCTGATGACTCCAGAGGTATGCAGAAACATCATGCCCTGGGGTCGA
TCAGCAGTCTCTTTAAGTCGACCCGTCGTGGCTGCAAACCCCTCAAACGTCGTTGTT
TCAATGATAAAGAATGCTGCAGCAAATTTTGCAATTCAGTCCGAAACCAGTGTGGA
TAAATGGCTAAAAACTGAATAAAAG (SEQ ID NO:228)

Translation:
MKLTCVVIVAVLVLTACQLITADDSRGMQKHHALGSISSLFKSTRRGCKPLKRRCFNDK
ECCSKFCNSVRNQCG (SEQ ID NO:229)

Toxin Sequence:
Arg-Gly-Cys-Lys-Xaa3-Leu-Lys-Arg-Arg-Cys-Phe-Asn-Asp-Lys-Xaa1-Cys-Cys-Ser-Lys-Phe-
Cys-Asn-Ser-Val-Arg-Asn-Gln-Cys-# (SEQ ID NO:230)

Name: w-RVIA
Species: radiatus
Cloned: Yes

DNA Sequence:

GGAATTCCGCTTGCACGGCGAACCTGACTTCATCTTTCTTCCCTGCCTCCTTTGGCAT
CACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGG
TCCTGACGGCCTGTCAACTCATCACAGCTGATGACTCCAGAGGTATGCAGAAGCAT
CATGCCCTGAGGTCGATCACCAAACTCTCCCTGTCGACTCGCTGCAAACCTCCCGGA
TCACCATGTAGAGTTTCTTCGTATAACTGCTGCTCTTCTTGCAAATCATACAACAAG
AAATGTGGCTGAACTTCCCCTTCTGTGCTCTATCCTTTTCCTGCCCGAGTCCTCCATA
CCTGAGAGTAGTCATGAACCACTGATTACCTACTCCTCTGGAGGGCCTCAGAGGAG
CTACTTTGAAATAAAAGCCCGCATTGCAAAAAAAAAA (SEQ ID NO:231)

Translation:

MKLTCVVIVAVLVLTACQLITADDSRGMQKHHALRSITKLSLSTRCKPPGSPCRVSSYN
CCSSCKSYNKKCG (SEQ ID NO:232)

Toxin Sequence:

Cys-Lys-Xaa3-Xaa3-Gly-Ser-Xaa3-Cys-Arg-Val-Ser-Ser-Xaa5-Asn-Cys-Cys-Ser-Ser-Cys-Lys-Ser-Xaa5-Asn-Lys-Lys-Cys-Gly-# (SEQ ID NO:233)

Name: Ra6.1
Species: rattus
Cloned: Yes

DNA Sequence:

GGATCCATGAAACTGACGTGCATGGTGATCATCGCCGTGCTGTTCCTGACAGCCTGT
CAATTCGATACAGCTGCGAGCTACGACAAAGGTAAGCAGAAACCTCCTACTCTGAG
GCCAGCTGACAAACACATCAGGTTGACCAAGCGTTGCAATGCTCGCAATGATGGTT
GCAGTCAACATTCTCAATGCTGCAGTGGATCTTGCAATAAGACTGCAGGCGTATGTC
TGTAAAGCTGGTCTGCCGTCTGATATTCCCTTTCTGTGCTTTATCCTCTTTTGCCTGA
GTCATCCATACCTGTGAATGGTTAAGAGCCACTCAATACCTACTCCTCTGGGGGCTT
CAGAGGAACTACATTAAATAAAGCCACATTGCAAAAAAAAAAAAAAAAAAAAA (SEQ ID NO:234)

Translation:

MKLTCMVIIAVLFLTACQFDTAASYDKGKQKPPTLRPADKHIRLTKRCNARNDGCSQH
SQCCSGSCNKTAGVCL (SEQ ID NO:235)

Toxin Sequence:

Cys-Asn-Ala-Arg-Asn-Asp-Gly-Cys-Ser-Gln-His-Ser-Gln-Cys-Cys-Ser-Gly-Ser-Cys-Asn-Lys-Thr-Ala-Gly-Val-Cys-Leu-^ (SEQ ID NO:236)

Name: Ra6.2
Species: rattus
Cloned: Yes

DNA Sequence:

GGATCCATGAAACTGACGTGCGTGGTGATCATCGCCGTGCTGTTCCTGACAGCCTGT
CAACTCGATGCAGCTGCGAGCTACGACAAAGGTAAGCAGAAACCTCCTACTCTGAG
GCCAGCTGACAAACACTTCAGGTTGATCAAGCGTTGCAATGCTCGCAATAGTGGTT
GCAGTCAACATCCTCAATGCTGCAGTGGATCTTGCAATAAGACTGCAGGCGTATGTC
TGTAAAGCTGGTCTGCCGTCTGATATTCCCTTTCTGTGCTTTATCCTCTTTTGCCTGA
GTCATCCATACCTGTGAATGGTTAAGAGCCACTCAATACCTACTCCTCTGGGGGCTT
CAGAGGAACTACATTAAATAAAGCCACATTGCAACGAAAAAAAAAAAAAAAAAAAA
(SEQ ID NO:237)

Translation:
MKLTCVVIIAVLFLTACQLDAAASYDKGKQKPPTLRPADKHFRLIKRCNARNSGCSQHP
QCCSGSCNKTAGVCL (SEQ ID NO:238)

Toxin Sequence:
Cys-Asn-Ala-Arg-Asn-Ser-Gly-Cys-Ser-Gln-His-Xaa3-Gln-Cys-Cys-Ser-Gly-Ser-Cys-Asn-
Lys-Thr-Ala-Gly-Val-Cys-Leu-^ (SEQ ID NO:239)

Name: Ra6.3
Species: rattus
Cloned: Yes

DNA Sequence:
GGATCCATGAAACTGACGTGTGTGGTGATCATCGCCGTGCTGTTCCTGACAGCCTGT
CAATTCGATACAGCTGCGAGCTACGACAAAGGTAAGCAGAAACCTCCTACTCTGAG
GCCAGCTGACAAACACTTCAGGTTGATCAAGCGTTGCAATGCTCGCAATAGTGGTT
GCAGTCAACATCCTCAATGCTGCAGTGGATCTTGCAATAAGACTTTGGGCGTATGTC
TGTAAAGCTGGTCTGCCGTCTGATATTCCCTTTCTGTGCTTTATCCTCTTTTGCCTGA
GTCATCCATACCTGTGAATGGTTAAGAGCCACTCAATACCTACTCCTCTGGGGGCTT
CAGAGGAACTACATTAAATAAAGCCACATTGAAAAAAAAAAAAAAAAAAAA (SEQ ID
NO:240)

Translation:
MKLTCVVIIAVLFLTACQFDTAASYDKGKQKPPTLRPADKHFRLIKRCNARNSGCSQHP
QCCSGSCNKTLGVCL (SEQ ID NO:241)

Toxin Sequence:
Cys-Asn-Ala-Arg-Asn-Ser-Gly-Cys-Ser-Gln-His-Xaa3-Gln-Cys-Cys-Ser-Gly-Ser-Cys-Asn-
Lys-Thr-Leu-Gly-Val-Cys-Leu-^ (SEQ ID NO:242)

Name: Sm6.1
Species: stercusmuscarum
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT

CCTGACGGCCTGTCAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATC
GTGCCCTGAGGTCGAAGACCAAACTCTCCATGTCGACTCGCTGCAAGAGTAAAGGA
GCAAAATGTTCAAGGCTTATGTATGACTGCTGCAGCGGTTCTTGCAGCGGCTACACA
GGTAGATGTGGCTGATCCAGCGCCTGATCTTCCCCCTTCTGTGCTCTATCCTTTTCTG
CCTGGGTCCTCCTTACCTGAGAGTGGTCATGAACCACTCATCACCTACTCCTCTGGA
GGCCTCAGAGGAGTTACAATGAAATAAAAGCCGCATTGC (SEQ ID NO:243)

Translation:

MKLTCVVIVAVLLLTACQLITADDSRGTQKHRALRSKTKLSMSTRCKSKGAKCSRLMY
DCCSGSCSGYTGRCG (SEQ ID NO:244)

Toxin Sequence:

Cys-Lys-Ser-Lys-Gly-Ala-Lys-Cys-Ser-Arg-Leu-Met-Xaa5-Asp-Cys-Cys-Ser-Gly-Ser-Cys-Ser-Gly-Xaa5-Thr-Gly-Arg-Cys-# (SEQ ID NO:245)

Name: Sm6.2
Species: stercusmuscarum
Isolated: Yes

Toxin Sequence:

Thr-Thr-Ser-Cys-Met-Gln-Ala-Gly-Ser-Xaa5-Cys-Gly-Ser-Thr-Thr-Arg-Ile-Cys-Cys-Gly-Xaa5-Cys-Ala-Xaa5-Phe-Gly-Lys-Lys-Cys-Ile-Asp-Xaa5-Xaa3-Ser-Asn-^ (SEQ ID NO:246)

Name: Sm6.3
Species: stercusmuscarum
Cloned: Yes

DNA Sequence:

ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGACCTGTCAACTCATCACAGCTGATGACTCCAGAGGTACGCAGGAGCATC
GTGCCCTGAGGTCGAAGACCAAACTCTCCATGTTAACTTTGCGCTGCGCATCTTACG
GAAAACCTTGTGGTATTGACAACGACTGCTGCAATGCATGCGATCCAGCCAGAAAT
ATATGTACGTAGCTGATCCGGCGTCTGATCTTCCCCCTTCTGTGCTCTATCCTTTTCT
GCCTGAGTCCTCCTTACCTGAGAGTGGTCATGAACCACTCATCATCTACTCTCCTGG
AGGCCTCAGAGGAGCTACAATGAAATAAAAGCCGCATTGC (SEQ ID NO:247)

Translation:

MKLTCVVIVAVLLLTTCQLITADDSRGTQEHRALRSKTKLSMLTLRCASYGKPCGIDND
CCNACDPARNICT (SEQ ID NO:248)

Toxin Sequence:

Cys-Ala-Ser-Xaa5-Gly-Lys-Xaa3-Cys-Gly-Ile-Asp-Asn-Asp-Cys-Cys-Asn-Ala-Cys-Asp-Xaa3-Ala-Arg-Asn-Ile-Cys-Thr-^ (SEQ ID NO:249)

Name: Sm6.4
Species: stercusmuscarum
Cloned: Yes

DNA Sequence:
GGATCCATGAAACTGACGTGTGTGGTGATTGTCGCCGTGCTGCTCCTGACGGCCTGT
CAACTCATCACAGCTGATGACTCCAGAGGTACGCAGGAGCATCGTGCCCTGAGGTC
GAAGACCAAACTCTCCATGTTAACTTTGCGCTGCGTATCTTACGGAAAACCTTGTGG
TATTGACAACGACTGCTGCAATGCATGCGATCCAGCCAGAAATATATGTACGTAGC
TGATCCGGCGTCTGATCTTCCCCCTTCTGTGCTCTATCCTTTTCTGCCTGGGTCCTCC
TTACCTGAGAGTGGTCATGAACCACTCATCACCTACTCCTCTGGAGGCCTCAGAGGA
GTTACAATGAAATAAAAGCCGCATTGCAAAAAAAAAAAAAAAAAAAAA (SEQ ID NO:250)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQEHRALRSKTKLSMLTLRCVSYGKPCGIDND
CCNACDPARNICT (SEQ ID NO:251)

Toxin Sequence:
Cys-Val-Ser-Xaa5-Gly-Lys-Xaa3-Cys-Gly-Ile-Asp-Asn-Asp-Cys-Cys-Asn-Ala-Cys-Asp-Xaa3-Ala-Arg-Asn-Ile-Cys-Thr-^ (SEQ ID NO:252)

Name: S6.1
Species: striatus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATC
GTTCCCTGAGGTCGACCACCAAAGTCTCCAAGGCGACTGACTGCATTGAAGCCGGA
AATTATTGCGGACCTACTGTTATGAAAATCTGCTGCGGCTTTTGCAGTCCATACAGC
AAAATATGTATGAACTATCCCAAAAATTGATCTTCCCCC (SEQ ID NO:253)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQKHRSLRSTTKVSKATDCIEAGNYCGPTVM
KICCGFCSPYSKICMNYPKN (SEQ ID NO:254)

Toxin Sequence:
Ala-Thr-Asp-Cys-Ile-Xaa1-Ala-Gly-Asn-Xaa5-Cys-Gly-Xaa3-Thr-Val-Met-Lys-Ile-Cys-Cys-Gly-Phe-Cys-Ser-Xaa3-Xaa5-Ser-Lys-Ile-Cys-Met-Asn-Xaa5-Xaa3-Lys-Asn-^ (SEQ ID NO:255)

Name: S6.2
Species: striatus
Cloned: Yes

DNA Sequence:
GTCGACTCGCTGCAAGCTTAAAGGACAATCATGTCGTAGGACTATGTATGACTGCTG
CAGCGGTTCTTGCGGCAGGAGAGGTAAATGTGGCTGATCCAGCGCCTGATCTCCCC
CCTTCTGTGCTCTATCCTTTTCTGCCTGGGTCCTCCTTACCTGAGAGTGGTCATGAAC
CACTCATCACCTACTCCTCTGGAGGCCTCAGAGGAGCTACAATGAAATAAAAGCCG
CATTGC (SEQ ID NO:256)

Translation:
STRCKLKGQSCRRTMYDCCSGSCGRRGKCG (SEQ ID NO:257)

Toxin Sequence:
Cys-Lys-Leu-Lys-Gly-Gln-Ser-Cys-Arg-Arg-Thr-Met-Xaa5-Asp-Cys-Cys-Ser-Gly-Ser-Cys-Gly-Arg-Arg-Gly-Lys-Cys-# (SEQ ID NO:258)

Name: S6.3
Species: striatus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAACTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATC
GTGCCCTGAGGTCGGACACCAAACTCTCCATGTCGACTCGCTGCAAGGCTGCAGGA
AAATCATGCAGTAGGATTGCGTATAACTGCTGCACCGGTTCTTGCAGATCAGGTAA
ATGCGGCTGATCCAGCGCCTGATCTTCCCCCTTCTGTGCTCTATCCTTTCTGCCTGAG
TCCTCTTACCTGAGAGTGGTCATGAACC (SEQ ID NO:259)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQKHRALRSDTKLSMSTRCKAAGKSCSRIAYN
CCTGSCRSGKCG (SEQ ID NO:260)

Toxin Sequence:
Cys-Lys-Ala-Ala-Gly-Lys-Ser-Cys-Ser-Arg-Ile-Ala-Xaa5-Asn-Cys-Cys-Thr-Gly-Ser-Cys-Arg-Ser-Gly-Lys-Cys-# (SEQ ID NO:261)

Name: S6.6
Species: striatus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAACTCATCACAGCTGATGACTCCAGAGGTACGCAGGAGCATC
GTGCCCTGAGGTCGGACACCAAACTCTCCATGTTAACTTTGCGCTGCGAATCTTACG
GAAAACCTTGTGGTATTTACAACGACTGCTGCAATGCATGCGATCCAGCCAAAAAG
ACATGTACGTAGCTGATCCGGCGTCTGATCT (SEQ ID NO:262)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQEHRALRSDTKLSMLTLRCESYGKPCGIYND
CCNACDPAKKTCT (SEQ ID NO:263)

Toxin Sequence:
Cys-Xaa1-Ser-Xaa5-Gly-Lys-Xaa3-Cys-Gly-Ile-Xaa5-Asn-Asp-Cys-Cys-Asn-Ala-Cys-Asp-Xaa3-Ala-Lys-Lys-Thr-Cys-Thr-^ (SEQ ID NO:264)

Name: w-SVIA
Species: striatus
Cloned: Yes

DNA Sequence:
ACTAGGTCCTCCGGCAGCCCCTGTGGTGTTACTAGTATATGCTGTGGTAGATGCTAT
AGGGGTAAATGTACGTAGCTCATCGGGCGTCTGATCTTCCCCCTTCTGTGCTCCATC
CTTTTCTGCCTGAGTCCTCCTTACCTGAGAGTGGTCGTGAACCACTCATCGCCTACTC
CTCTGGAGGCTTCAGAGGGGCTACACTAAAATAAAAGCTATATTGCAATGAAAAAA
A (SEQ ID NO:265)

Translation:
CRSSGSPCGVTSICCGRCYRGKCT (SEQ ID NO:266)

Toxin Sequence:
Cys-Arg-Ser-Ser-Gly-Ser-Xaa3-Cys-Gly-Val-Thr-Ser-Ile-Cys-Cys-Gly-Arg-Cys-Xaa5-Arg-Gly-Lys-Cys-Thr-# (SEQ ID NO:267)

Name: w-SVIB
Species: striatus
Isolated: Yes

Toxin Sequence:
Cys-Lys-Leu-Lys-Gly-Gln-Ser-Cys-Arg-Lys-Thr-Ser-Xaa5-Asp-Cys-Cys-Ser-Gly-Ser-Cys-Gly-Arg-Ser-Gly-Lys-Cys-# (SEQ ID NO:268)

Name: Sx6.1
Species: striolatus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGTCTTGCTGCTC
CTGACGACCTGTCGTCTCATCACAGCTGATGACTCCAGAGGTACGCAGAAGCATCG
TTCCCTGAGGTCGACTACTAAAGTCTCCATGTCGACTCGCTGCAAGGGTAAAGGAG
CATCATGTCTTAGGACTGCGTATGACTGCTGCACCGGTTCTTGCAACAGAGGTAGAT

GTGGCTGATCCAGCGTCTGATCTTCCCCCTTCTGTGCTCTATCCTTTTCTGCTTGAGT
CCTCCTTA (SEQ ID NO:269)

Translation:
MKLTCVVIVVLLLLTTCRLITADDSRGTQKHRSLRSTTKVSMSTRCKGKGASCLRTAYD
CCTGSCNRGRCG (SEQ ID NO:270)

Toxin Sequence:
Cys-Lys-Gly-Lys-Gly-Ala-Ser-Cys-Leu-Arg-Thr-Ala-Xaa5-Asp-Cys-Cys-Thr-Gly-Ser-Cys-
Asn-Arg-Gly-Arg-Cys-# (SEQ ID NO:271)

Name: Sx6.2
Species: striolatus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTTCTGCTG
ACGGCGTGTCAACTCATCACAGCTGAGGACTCCAGAGGTACACAGAAGCATCGTAC
CCTGAGGTCGACCGTCAGACGCTCCAAGTCCGAGTTGACTACGAGATGCAGGCCTT
CAGGATCCAACTGTGGTAATATTAGTATCTGCTGTGGTAGATGCGTTAACAGAAGAT
GTACGTAGCTCATCGGGCGTCTGATCTTTCCCC (SEQ ID NO:272)

Translation:
MKLTCVVIVAVLLTACQLITAEDSRGTQKHRTLRSTVRRSKSELTTRCRPSGSNCGNISI
CCGRCVNRRCT (SEQ ID NO:273)

Toxin Sequence:
Cys-Arg-Xaa3-Ser-Gly-Ser-Asn-Cys-Gly-Asn-Ile-Ser-Ile-Cys-Cys-Gly-Arg-Cys-Val-Asn-Arg-
Arg-Cys-Thr-^ (SEQ ID NO:274)

Name: Sx6.3
Species: striolatus
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTTCTGTTC
CTGACGGCGTGTCAACTCATCACAGCTGAGGACTCCAGAGGTACACAGAAGCATCG
TTCCCTGAGGTCGACTACCAAAGTCTCCAAGTCGACTAGCTGCATGAAAGCCGGGT
CTTATTGCGTCGCTACTACGAGAATCTGCTGCGGTTATTGCGCTTATTTCGGCAAAA
TATGTATTGACTATCCCAAAAACTGATCTTCCCCCTACTGTGCTCTATCCTTTT (SEQ
ID NO:275)

Translation:
MKLTCVVIVAVLFLTACQLITAEDSRGTQKHRSLRSTTKVSKSTSCMKAGSYCVATTRI
CCGYCAYFGKICIDYPKN (SEQ ID NO:276)

Toxin Sequence:
Ser-Thr-Ser-Cys-Met-Lys-Ala-Gly-Ser-Xaa5-Cys-Val-Ala-Thr-Thr-Arg-Ile-Cys-Cys-Gly-Xaa5-Cys-Ala-Xaa5-Phe-Gly-Lys-Ile-Cys-Ile-Asp-Xaa5-Xaa3-Lys-Asn-^ (SEQ ID NO:277)

Name: Tx6.15
Species: textile
Cloned: Yes

DNA Sequence:
GTTGACTCGGTACTGCACGCCTCATGGAGGACATTGTGGTTATCATAATGACTGCTG
CAGTCATCAATGCAATATAAACAGAAATAAATGTGAGTAGCTGATCTGGCATCTGA
TCTGTGCTCGTCCTTACCTGAGAGTGGTCATGAACCACTCATCACCTACTCCTCTGG
AGGC (SEQ ID NO:278)

Translation:
LTRYCTPHGGHCGYHNDCCSHQCNINRNKCE (SEQ ID NO:279)

Toxin Sequence:
Xaa5-Cys-Thr-Xaa3-His-Gly-Gly-His-Cys-Gly-Xaa5-His-Asn-Asp-Cys-Cys-Ser-His-Gln-Cys-Asn-Ile-Asn-Arg-Asn-Lys-Cys-Xaa1-^ (SEQ ID NO:280)

Name: w-Tx
Species: textile
Isolated: Yes

Toxin Sequence:
Xaa5-Cys-Thr-Xaa3-Xaa5-Gly-Gly-His-Cys-Gly-Xaa5-His-Asn-Asp-Cys-Cys-Ser-His-Gln-Cys-Asn-Ile-Asn-Arg-Asn-Lys-Cys-Xaa1-^ (SEQ ID NO:281)

Name: C. tulipa w2
Species: tulipa
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAGCTCATCACAGCTCTGCACTCCAGAGGTACGCAGAAGCATC
GTGCCCTGGGGCGGACCACCAAACTCACCTTGTCGACTCGCTGCAAATCACCCGGA
TCTCCATGTTCACCGACTAGTTATAATTGCTGCTGGTCTTGCAGTCCATACAGAAAA
AAATGTAGGGGCTAATCCAGCGCCTGATTTTCCCCCTTCTGTGCTCTATTCCTTTCTG
CCTGAGTCCTCCTTACCTGAAAGTGGTCATGAACCACTCATCACCTACTTCTCTGGA
GGCTTCGGAGGAGCTACATTGAAATAAAAGCCGCATTGC (SEQ ID NO:282)

Translation:

MKLTCVVIVAVLLLTACQLITALHSRGTQKHRALGRTTKLTLSTRCKSPGSPCSPTSYNC CWSCSPYRKKCRG (SEQ ID NO:283)

Toxin Sequence:
Cys-Lys-Ser-Xaa3-Gly-Ser-Xaa3-Cys-Ser-Xaa3-Thr-Ser-Xaa5-Asn-Cys-Cys-Xaa4-Ser-Cys-Ser-Xaa3-Xaa5-Arg-Lys-Lys-Cys-Arg-# (SEQ ID NO:284)

Name: w-TVIA
Species: tulipa
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAGCTCATCACAGCTCTGCACTCCAGAGGTACGCAGAAGCATC
GTGCCCTGGGGTCGACCACCAAACTCACCTTGTCGACTCGCTGCTTGTCACCCGGAT
CTTCATGTTCACCGACTAGTTATAATTGCTGCAGGTCTTGCAATCCATACAGCAGAA
AATGTAGGGGCTAATCCAGCGCCTGATCTTCCCCCTTCTGTGCTCTATTCCTTTCTGC
CTGAGTCCTCCTTACCTGAAAGTGGTCATGAACCACTCATCACCTACTTCTCTGGAG
GCTTCGGAGGAGCTACATTGAAATAAAAGCCGCATTGC (SEQ ID NO:285)

Translation:
MKLTCVVIVAVLLLTACQLITALHSRGTQKHRALGSTTKLTLSTRCLSPGSSCSPTSYNC CRSCNPYSRKCRG (SEQ ID NO:286)

Toxin Sequence:
Cys-Leu-Ser-Xaa3-Gly-Ser-Ser-Cys-Ser-Xaa3-Thr-Ser-Xaa5-Asn-Cys-Cys-Arg-Ser-Cys-Asn-Xaa3-Xaa5-Ser-Arg-Lys-Cys-Arg-# (SEQ ID NO:287)

Name: Vi6.1
Species: viola
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAGCTCATTACAGCTGATGACTCCAGAGGTACGCAGTTGCATCG
TGCCCTGAGGAAGGCCACCAAACTCCCCGTGTCGACTCGCTGCATTACTTTAGGAAC
ACGATGTAAGGTTCCGAGTCAATGCTGCAGATCTTCTTGCAAGAACGGTCGTTGTGC
TCCATCCCCTGAAGAATGGTAAATGTGGCTGATCCAGCGCCTGATCTTCCCCCTTCT
GACTGTCTCCGACCTTTTCTGCCTGAGTCCTCCTTACCTGAGAGGTGTCATGAACCA
CTCATCACCTACTCCCCTGGAAGCTTCAGAGGAGCTACATTGAAATAAAAGCCGCA
TTGC (SEQ ID NO:288)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQLHRALRKATKLPVSTRCITLGTRCKVPSQC CRSSCKNGRCAPSPEEW (SEQ ID NO:289)

Toxin Sequence:
Cys-Ile-Thr-Leu-Gly-Thr-Arg-Cys-Lys-Val-Xaa3-Ser-Gln-Cys-Cys-Arg-Ser-Ser-Cys-Lys-Asn-Gly-Arg-Cys-Ala-Xaa3-Ser-Xaa3-Xaa1-Xaa1-Xaa4-^ (SEQ ID NO:290)

Name: Vi6.2
Species: viola
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAGCTCATTATAGCTGGGGACTCCAGAGGTACGCAGTTGCATCG
TGCCCTGAGGAAGGCCACCAAACTCTCCGTGTCGACTCGCTGCAAGAGTAGAGGAT
CATCATGTCGTAGGACTTCGTATGACTGCTGCACGGGTTCTTGCAGAAATGGTAAAT
GTGGCTGATCCAGCGCCTGATCTTCCCCCTTCTGTGCTCCATCCTTTTCTGCCTGAGT
CCTCCTTACCTGAGAGTGGGCATGAACCACTCATCACCTACTCCCTGGAAGCTTCAG
AGGAGCTACATTGAAATAAAAGCCGCATTGC (SEQ ID NO:291)

Translation:
MKLTCVVIVAVLLLTACQLIIAGDSRGTQLHRALRKATKLSVSTRCKSRGSSCRRTSYD
CCTGSCRNGKCG (SEQ ID NO:292)

Toxin Sequence:
Cys-Lys-Ser-Arg-Gly-Ser-Ser-Cys-Arg-Arg-Thr-Ser-Xaa5-Asp-Cys-Cys-Thr-Gly-Ser-Cys-Arg-Asn-Gly-Lys-Cys-# (SEQ ID NO:293)

Name: Vi6.3
Species: viola
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGCGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAGCTCATTACAGCTGAAGACTCCAGAGGTACGCATGAGCATC
TTGCCCTGAAGTCGACCTCCAAAGTCTCCAAGTCGACTAGCTGCATGGAAGCCAGA
TCTTATTGCGGACCTGCTACTACGAAAATCTGCTGCGATTTTTGCAGTCCATTCAGC
GATAGATGTATGAACAATCCCAACAATTGATCTTCCCCCTTGTGTGCTCCATCTTTTC
TGCCTGAGTCCTCCTTACCTGAGAGTGGTCATGAACCACTCATCACCTACTCCTCTG
GAGGCTTCAGAGGAGTTACATTGAAATAAAAGCCGCATGC (SEQ ID NO:294)

Translation:
MKLTCVAIVAVLLLTACQLITAEDSRGTHEHLALKSTSKVSKSTSCMEARSYCGPATTKI
CCDFCSPFSDRCMNNPNN (SEQ ID NO:295)

Toxin Sequence:
Ser-Thr-Ser-Cys-Met-Xaa1-Ala-Arg-Ser-Xaa5-Cys-Gly-Xaa3-Ala-Thr-Thr-Lys-Ile-Cys-Cys-

Asp-Phe-Cys-Ser-Xaa3-Phe-Ser-Asp-Arg-Cys-Met-Asn-Asn-Xaa3-Asn-Asn-^ (SEQ ID NO:296)

Name: Vi6.4
Species: viola
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGCT
CCTGACGGCCTGTCAGCTCATTACAGCTGAGGACTCCAGAGGTACGCAGTTGCATC
GTGCCCTGAGGAAGACCACCAAACTCTCCTTGTCGACTCGCTGCAAGGGTCCAGGA
GCCATATGTATAAGGATTGCGTATAACTGCTGCAAGTATTCTTGCGGAAATGGTAAA
TGTGGCTGATCCAGCGCCTGATCTTCCCCCTTGTGTGCTCCATCCTTTTTCTGCCTGA
GTCCTCCTTACCTGAGAGTGGTCATGAACCACTCATCACCTACTCCTCTGGAGGCTT
CAGAGGAGCTACATTGAAATAAAAGCCGCATGC (SEQ ID NO:297)

Translation:
MKLTCVVIVAVLLLTACQLITAEDSRGTQLHRALRKTTKLSLSTRCKGPGAICIRIAYNC
CKYSCGNGKCG (SEQ ID NO:298)

Toxin Sequence:
Cys-Lys-Gly-Xaa3-Gly-Ala-Ile-Cys-Ile-Arg-Ile-Ala-Xaa5-Asn-Cys-Cys-Lys-Xaa5-Ser-Cys-Gly-Asn-Gly-Lys-Cys-# (SEQ ID NO:299)

Name: Vi6.5
Species: viola
Cloned: Yes

DNA Sequence:
ACCAAAACCATCATCAAAATGAAACTGACGTGTGTGGTGATCGTCGCCGTGCTGTTC
CTGACGGCCTGTCAATTCATCACAGCTGATGACTCCAGAAGTACGCAGAAGCATCG
TGCCCTGAGGTCGACCACCAAACACTTTATGTTGACTTGGTACTGCACGCCTTATGG
AGGACATTGTGGTTATTATAATGACTGCTGCAGTCATCAATGCAATATAAACAGAA
ATAAATGTGAGTAGCTGATCCGGCATCTGATCTGTGCTCGCCCTAACCTGAGAGTGG
TCATGAACCACTCATCATCTACTCCTCTGGAGGCTTCAGAGGAGCTACATGGAAATA
AAAGCCGCATTGC (SEQ ID NO:300)

Translation:
MKLTCVVIVAVLFLTACQFITADDSRSTQKHRALRSTTKHFMLTWYCTPYGGHCGYYN
DCCSHQCNINRNKCE (SEQ ID NO:301)

Toxin Sequence:
Xaa5-Cys-Thr-Xaa3-Xaa5-Gly-Gly-His-Cys-Gly-Xaa5-Xaa5-Asn-Asp-Cys-Cys-Ser-His-Gln-Cys-Asn-Ile-Asn-Arg-Asn-Lys-Cys-Xaa1-^ (SEQ ID NO:302)

Name: Pu6.4
Species: pulicarius
Cloned: Yes

DNA Sequence:
GGATCCATGAAACTGACGTGCGTGGTGATTATCGCCGTGCTGTTCCTGACGGCCTGT
CAACTCATTACAGCTGAGACTTACTCCAGAGGTAAGCAGATGCACCGTGCTCTGAG
GTCAACTGACAAAAACTCCAAGTTGACCAGGGAATGCACACCTCCAGATGGAGCTT
GTGGTTTACCTACACACTGCTGCGGGTTTTGCGATATGGCAAACAACAGATGTCTGT
AAAGCGTCTGATATTCCCCTTCTGTGCTCTATCCTCTTTGGCCTGAGTCATCCATACC
TGTGCTCGAG (SEQ ID NO:303)

Translation:
MKLTCVVIIAVLFLTACQLITAETYSRGKQMHRALRSTDKNSKLTRECTPPDGACGLPT
HCCGFCDMANNRCL (SEQ ID NO:304)

Toxin Sequence:
Xaa1-Cys-Thr-Xaa3-Xaa3-Asp-Gly-Ala-Cys-Gly-Leu-Xaa3-Thr-His-Cys-Cys-Gly-Phe-Cys-
Asp-Met-Ala-Asn-Asn-Arg-Cys-Leu-^ (SEQ ID NO:305)

Name: Pu6.6
Species: pulicarius
Cloned: Yes

DNA Sequence:
GGATCCATGAAACTGACGTGCGTGGTGATTATCGCCGTGCTGTTCCTGACGGCCTGT
CAACTCATTACAGCTGAGACTTACTCCAGAGGTAAGCAGATGCACCGTGCTCTGAG
GTCAACTGACAAAAACTCCCAGTTGACCAGGGAATGCACACCTCCAGGTGGAGCTT
GTGGTTTACCTACACACTGCTGCGGGTTTTGCGATATGGCAAACAACAGATGTCTGT
AAAGCGTCTGATATTCCCCTTCTGTGCTCTATCCTCTTTGGCCTGAGTCATCCATACC
TGTGCTCGAG (SEQ ID NO:306)

Translation:
MKLTCVVIIAVLFLTACQLITAETYSRGKQMHRALRSTDKNSQLTRECTPPGGACGLPT
HCCGFCDMANNRCL (SEQ ID NO:307)

Toxin Sequence:
Xaa1-Cys-Thr-Xaa3-Xaa3-Gly-Gly-Ala-Cys-Gly-Leu-Xaa3-Thr-His-Cys-Cys-Gly-Phe-Cys-
Asp-Met-Ala-Asn-Asn-Arg-Cys-Leu-^ (SEQ ID NO:308)

Name: Ra6.4
Species: rattus
Cloned: Yes

DNA Sequence:
GGATCCATGAAACTGACGTGTGTGGTGATCATCGCCGTGCTGTTCCTGGCAGCCTGT
CAACCTGTTACAACTGAGACTTTCTCCAGAGGTAAGGAGAAGCGTCGTGCTCTGAG
GTCAACTGACGGCAACTCCCGGTTGACCAGGGCATGCACGCCTGAAGGTGGAGCCT
GTAGTAGTGGGCGTCACTGCTGCGGCTTTTGCGATAACGTGTCCCACACGTGCTATG
GTGAAACACCATCTCTCCACTGATGTTTCCCCTTCTGTGCTCTATCTTCTTTTGCCTG
AGTCATCCATACCTGTGCTCGAG (SEQ ID NO:309)

Translation:
MKLTCVVIIAVLFLAACQPVTTETFSRGKEKRRALRSTDGNSRLTRACTPEGGACSSGR
HCCGFCDNVSHTCYGETPSLH (SEQ ID NO:310)

Toxin Sequence:
Ala-Cys-Thr-Xaa3-Xaa1-Gly-Gly-Ala-Cys-Ser-Ser-Gly-Arg-His-Cys-Cys-Gly-Phe-Cys-Asp-
Asn-Val-Ser-His-Thr-Cys-Xaa5-Gly-Xaa1-Thr-Xaa3-Ser-Leu-His-^ (SEQ ID NO:311)

Name: Sm6.7
Species: stercusmuscarum
Cloned: Yes

DNA Sequence:
AGATCCATGAAACTGACGTGCGTGGTGATCGTCGCCGTGCTGCTCCTGACGGCCTGT
CAACTCATCACAGCTGATGACTCCAGAGGTACGCAGGAGCATCGTGCCCTGAGGTC
GGACACCAAACTCCCCATATCGACTCGCTGCAAGGGTAAAGGAGCATCATGTCATA
AGACTATGTATGACTGCTGCAGCGGTTCCTGCACCAGAGGTAGATGTGGCTGATCC
AGCGCCTGATCTTCCCCCTTCTGTGCTCTATCCTTTTCTGCCTGAGTCATCATACCTG
TGCTCGAGCGTTACTAGTGGATCCGAGCTCGGTACCAAGCTTGGCGTAATCATAAA
ANC (SEQ ID NO:312)

Translation:
MKLTCVVIVAVLLLTACQLITADDSRGTQEHRALRSDTKLPISTRCKGKGASCHKTMYD
CCSGSCTRGRCG (SEQ ID NO:313)

Toxin Sequence:
Cys-Lys-Gly-Lys-Gly-Ala-Ser-Cys-His-Lys-Thr-Met-Xaa5-Asp-Cys-Cys-Ser-Gly-Ser-Cys-Thr-
Arg-Gly-Arg-Cys-# (SEQ ID NO:314)

Xaa1 = Glu or γ-Carboxy Glu
Xaa2 = Gln or pyroGlu
Xaa3 = Pro or Hydroxy Pro
Xaa4 = Trp or Bromo Trp
Xaa5 = Tyr, ^{125}I-Tyr, mono-iodo-Tyr or di-iodo-Tyr or O-sulpho-Tyr or O-Phospho-Tyr
^ = Free-carboxyl C-term or Amidated C-term, preferably Free-carboxyl

= Free-carboxyl C-term or Amidated C-term, preferably Amidated

TABLE2

Alignment of ω-Conopeptides (SEQ ID NO:)

Ar6.10	(F170)	---QCSANGGSC-TRHFH---CCSLYCNKDSSVCVATSYP^ (315)
Ar6.2	(F074)	---TCNTPTEYC-TLHRH---CCSGYCHKTIQACS^ (316)
Ar6.3		---QCTPNGGSC-SRHFH---CCSLYCNKSTGVCIATSYP^ (317)
Ar6.4	(F009)	---TCNTPTEYC-TLHQH---CCSGYCHKTIQACS^ (318)
Ar6.6	(F069)	---ECTPPGGACGLPT-H---CC-GFCDTANNRCL^ (319)
Ar6.7	(F073)	---TCNTPTEYC-TLHQH---CCSGHCHKTIQACA^ (320)
Ar6.8	(F169)	---QCSPIGGYC-TLHIH---CCSNHCIKPIGRCVAT^ (321)
Ar6.9	(F171)	---QCLPNGGYC-TLHIH---CCSDHCIKPIDRCVAT^ (322)
Ay6.1	(A653)	----CKGKGKPCSRISYN---CCTGSCRS--GKC# (323)
Ay6.2	(A654)	----CMEAGSYCG-STTR--ICC-GFCAYFGKKCIDYPSN^ (324)
Ay6.3	(J419)	----CKAKGKPCSRIAYN---CCTGSCRS--GKC# (325)
Ay6.4		----CASYGKPCGIDN-D---CCNA-CDPGRNICT^ (326)
Bu6.1		-STSCMEAGSYCGPATTK--ICC-DFCSPFSDRCMNNPNN^ (327)
Bu6.2		----CITPGTRCKVPS-Q---CCRGPCKNGR--CTPSPSEW^ (328)
Bu6.3		----CATYGKPCGIQN-D---CC-NTCDPARRTCT^ (329)
Bu6.4		----CKGPGASCIRIAYN---CCKYSCRN--GKC# (330)
Bu6.5		-STSCMAAGSYCGPATTN--ICC-DFCSPFSDRCMKKPNN^ (331)
Bu6.6		----CKSKGSSCHRTSYD---CCTGSCRN--GRC# (332)
C6.1		----CKSTGASCRRTSYD---CCTGSCRS--GRC# (333)
C6.4		----CQGRGASCRKTMYN---CCSGSCN--RGSC# (334)
C6.5		----CLPAGESCLFSRIR---CC-GTCSSVLKSCVS^ (335)
C6.6		----CQGRGGPCTKAVFN---CCSGSCN--RGRC# (336)
C6.7		----CATYGKPCGIQN-D---CC-NTCDPARKTCT^ (337)
C6.8		----CRGRGGPCTKAMFN---CCSGSCN--RGRC# (338)
Ca6.4	(F168)	---QCSANGGSC-TRHFH---CCSLYCNKDSSVCVATSYP^ (339)
Cn6.1		----CASYGKPCGIDN-D---CC-NTCDPARKTCT^ (340)
Cn6.2	(I583)	----CKGTGKPCSRIAYN---CCTGSCRS--GKC# (341)
Cn6.3		-ATDCIEAGNYCGPTVMK--ICC-GFCSPYSKICMNYPQN^ (342)
Cn6.4		----CKGKGASCTRLMYD---CCHGSCSSSKGRC# (343)
Cn6.5	(I590)	----CKGKGASCHRTSYD---CCTGSCN--RGKC# (344)
Cn6.6	(I584)	----CASYGKPCGIYN-D---CC-NTCDPARKTCT^ (345)
Cn6.7	(J409)	----CKGTGKPCSRVAYN---CCTGSCRS--GKC# (346)
Cn6.8	(J407)	-STSCMKAGSYCR-STTR--TCC-GYCAYFGKFCIDFPSN^ (347)
Cr6.1		----CKGKGASCRKTMYN---CCSGSCSN--GRC# (348)
Cr6.2		-STSCMEAGSYCR-STTR--TCC-GYCSYFSKKCIDFPSN^ (349)
Cr6.3		----CKSKGAKCSRLMYD---CCSGSCSRYSGRC# (350)
Cr6.4		-STGCMKAGSYCR-STTR--TCC-GYCAYFGKKCIDYPSN^ (351)
Da6.8		---SCTPPGGPCGYYN-D---CCSHQCNISRNKCE^ (352)
Di6.1		----CEDOGEOCGSDH-S---CCGGSCN--HNVCA^ (353)
E6.2		---PCKPKGRKCFPHQKD---CCNKTCT--RSKCP^ (354)
E6.3		---ACWSSGTPCGTDS-L---CCGG-CNVSKSKCN^ (355)
G6.1	(J420)	----CKSPGSSCSPTSYN---CCR-SCNPYAKRCY# (356)
G6.2	(J423)	----CKSPGTPCSRGMRD---CCT-PCLLYSNKC-R--RY^ (357)
J410		----CLSPGSRCHKTMRN---CCT-SCSSYKGKCRP--RK^ (358)
J411		----CKPPGRKCLNRKNE---CCSKFCNEHLHMC# (359)

	J413	----CKPPRRKCLKIKDK---CC-NFCNTHLNMC# (360)
	J414	----CAGPGTIC--PNRV---CC-GYCSKRTHLCHS---RT# (361)
	La6.1	---KCWPSGSYCRANS-K---CCSG-CDRNRNKCY^ (362)
	La6.2	----CLPPGSYCK-ATTE--VCCS-SCLQFAQIC-----S# (363)
5	L6.1	----CKSPGSPCSVTSYN---CCT-FCSSYTKKCRA--SL^ (364)
	L6.2	----CAGPGAIC--PNRV---CC-GYCSKRTHLCHS---RT# (365)
	L6.3	---ACWSSGTPCGTDS-L---CCGG-CNVSKSKCN^ (366)
	L6.4	---KCWSPGTYCRAHS-K---CCRG-CDQNRNKCY^ (367)
	La6.3	----CKSPGSSCSVSMRN---CCT-SCNSRTKKCTR--R# (368)
10	La6.4	---TCWPSGTACGIDS-N---CCSG-CNVSRSKCN^ (369)
	La6.5	---KCWPSGSYCRANS-K---CCSG-CDRNRSKCN^ (370)
	Lp6.1 (JG4)	SLFECAPSGGRCGFLK-S---CCEGYCDGESTSCVSGPYSI^ (371)
	Lp6.2 (JG5)	WPLDCTAPSQPCGYFP-R---CCG-HCDV-RRVCTS# (372)
	Lp6.3 (JG7)	----CMSPGGICGDFG-D---CCE-ICNV-YGICVSDLPGI^ (373)
15	Lp6.4 (JG15)	---YCAPPGGACGFFD-H---CC-GYCETFYNTC-R^ (374)
	M6.1	----CKGTGKPCSRIAYN---CCTGSCRS--GKC# (375)
	M6.2	----CASYGKPCGIYN-D---CC-NTCDPARKTCT^ (376)
	Mi6.1 (F157)	----CNDRGGGC-SQHPH---CCGGTCNKLIGVCL^ (377)
	Mn6.1	----CKSTGKSCSRIAYN---CCTGSCRS--GKC# (378)
20	Mn6.2	----CKGKGSSCSRTMYN---CCTGSCN--RGKC# (379)
	O6.1	-SPPCMKGGSSCR-GTTG--VCC-GFCSDFGYKCRDYPQN^ (380)
	O6.2	----CLPDGTSCLFSRIR---CC-GTCSSILKSCVS^ (381)
	P6.1	---OCKTOGRKCFOHQKD---CCGRACI--ITICP^ (382)
	P6.2	---SCKLOGAYCNAXDYD---CCLR-CKV-GGTC# (383)
25	P6.3	---PCKKTGRKCFPHQKD---CCGRACI--ITICP^ (384)
	Pu6.2 (JG28)	---QCSPNGGSC-SRHFH---CCSLYCNKNTGVCIAT^ (385)
	Pu6.4 (AA678)	---ECTPPDGACGLPT-H---CC-GFCDMANNRCL^ (386)
	Pu6.6 (AA681)	---ECTPPGGACGLPT-H---CC-GFCDMANNRCL^ (387)
	R6.1	--HGCKPLKRRCFNDKE----CCSKFCNSVRKQC# (388)
30	R6.2	--RGCKPLKRRCFNDKE----CCSKFCNSVRNQC# (389)
	Ra6.1 (F206)	----CNARNDGC-SQHSQ---CCSGSCNKTAGVCL^ (390)
	Ra6.2 (F205)	----CNARNSGC-SQHPQ---CCSGSCNKTAGVCL^ (392)
	Ra6.3 (F207)	----CNARNSGC-SQHPQ---CCSGSCNKTLGVCL^ (393)
	Ra6.4 (AA688)	---ACTPEGGACSSGR-H---CC-GFCDNVSHTCYGETPSLH^ (394)
35	S6.1	-ATDCIEAGNYCGPTVMK--ICC-GFCSPYSKICMNYPKN^ (395)
	S6.2	----CKLKGQSCRRTMYD---CCSGSCGR-RGKC# (396)
	S6.3	----CKAAGKSCSRIAYN---CCTGSCRS--GKC# (397)
	S6.6	----CESYGKPCGIYN-D---CC-NACDPAKKTCT^ (398)
	Sm6.1 (J428)	----CKSKGAKCSRLMYD---CCSGSCSGYTGRC# (399)
40	Sm6.2	-TTSCMQAGSYCG-STTR--ICC-GYCAYFGKKCIDYPSN^ (400)
	Sm6.3 (J429)	----CASYGKPCGIDN-D---CC-NACDPARNICT^ (401)
	Sm6.4 (J431)	----CVSYGKPCGIDN-D---CC-NACDPARNICT^ (402)
	Sm6.7 (AA689)	----CKGKGASCHKTMYD---CCSGSCTRG--RC# (403)
	Sx6.1	----CKGKGASCLRTAYD---CCTGSCN--RGRC# (404)
45	Sx6.2	----CRPSGSNCGNIS-I---CCGR-CVN--RRCT^ (405)
	Sx6.3	-STSCMKAGSYCV-ATTR--ICC-GYCAYFGKICIDYPKN^ (406)
	Tx6.15	---YCTPHGGHC-GYHND---CCSHQCNINRNKCE^ (407)
	Vi6.1	----CITLGTRCKVPS-Q---CCRSSCKN--GRCAPSPEEW^ (408)
	Vi6.2	----CKSRGSSCRRTSYD---CCTGSCRN--GKC# (409)
50	Vi6.3	-STSCMEARSYCGPATTK--ICC-DFCSPFSDRCMNNPNN^ (410)
	Vi6.4	----CKGPGAICIRIAYN---CCKYSCGN--GKC# (411)
	Vi6.5	---YCTPYGGHCGYYN-D---CCSHQCNINRNKCE^ (412)

ω-Tx	----**C**TPYGGH**C**GYNH-D---**CC**SHQ**C**NINRNK**C**E^ (413)
C. tulipa ω2	----**C**KSWGSO**C**SOTSTN---**CC**W-S**C**SPYRKK**C**-R# (414)

EXAMPLE 3

In vivo Activity of ω-Conopeptide Frings Audiogenic Seizure Susceptible Mice

[0079] *In vivo* anticonvulsant activity of ω-conopeptides is analyzed in Frings audiogenic seizure susceptible mice as described by White et al. (1992). The ω-conopeptides are found to have anticonvulsant activity in this assay.

EXAMPLE 4

In vivo Activity of ω-Conopeptides in CF No. 1 Mice

[0080] *In vivo* anticonvulsant activity of ωconopeptides is analyzed in CF No. 1 mice as described by White et al. (1995), using the maximal electroshock, subcutaneous pentylenetetrazole (Metrazol) seizure threshold and threshold tonic extension test. ω-Conopeptides are found to have anticonvulsant activity.

EXAMPLE 5

In Vivo Activity of ω-Conopeptides in Pentylenetetrazole-Induced Threshold Seizure Model

[0081] The *in vivo* activity of ω-conopeptides is analyzed using timed intravenous infusion of pentylenetetrazole (White et al., 1995). At time to peak effect, the convulsant solution (0.5% pentylenetetrazole in 0.9% saline containing 10 U.S.P. units/ml heparin sodium) is infused into the tail vein at a constant rate of 0.34 ml/min. The time in seconds from the start of the infusion to the appearance of the first twitch and the onset of clonus is recorded for each drug treated or control animal. The times to each endpoint are converted to mg/kg of pentylenetetrazole for each mouse, and mean and standard error of the mean are calculated. It is found that ω-conopeptides elevate the i.v. pentylenetetrazole seizure threshold.

EXAMPLE 6

In vivo Activity of ω-Conopeptides in Pain Models

[0082] The anti-pain activity of ω-conopeptides is shown in several animal models. These models include the nerve injury model (Chaplan, et al., 1997), the nocioceptive response

to s.c. formalin injection in rats (Codene, 1993) and an NMDA-induced persistent pain model (Liu, et al., 1997). In each of these models it is seen that the ω-conopeptides and ω-conopeptides derivatives have analgesic properties.

[0083] More specifically, this study evaluates the effect of intrathecal administration of ω-conopeptides in mice models of nocioceptive and neuropathic pain. For nocioceptive pain, the effect of the ω-conopeptides is studied in two different tests of inflammatory pain. The first is the formalin test, ideal because it produces a relatively short-lived, but reliable pain behavior that is readily quantified. There are two phases of pain behavior, the second of which is presumed to result largely from formalin-evoked inflammation of the hind paw. An ω-conopeptide is administered 10 minutes prior to injection of formalin. The number of flinches and/or the duration of licking produced by the injection is monitored. Since the first phase is presumed to be due to direct activation of primary afferents, and thus less dependent on long term changes in the spinal cord, ω-conopeptides are presumed to have greatest effect on the magnitude of pain behavior in the second phase.

[0084] The mechanical and thermal thresholds in animals that received an injection of complete Freund's adjuvant into the hind paw are also studied. This produces a localized inflammation including swelling of the hind paw and a profound decrease in mechanical and thermal thresholds, that are detected within 24 hours after injection. The changes in thresholds in rats that receive ω-conopeptides are compared with those of rats that receive vehicle intrathecal injections.

[0085] An important issue is whether the drugs are effective when administered after the pain model has been established, or whether they are effective only if used as a pretreatment. Clearly, the clinical need is for drugs that are effective after the pain has developed. To address this issue, animals are studied in which ω-conopeptides are administered repeatedly, after the inflammation (CFA) or nerve injury has been established. In these experiments, an ω-conopeptide is injected daily by the intrathecal (i.t.) route. The mechanical and thermal thresholds (measured, respectively, with von Frey hairs in freely moving animals and with the Hargreave's test, also in freely moving animals) are repeated for a 2 to 4 week period after the injury is induced and the changes in pain measured monitored over time.

EXAMPLE 7

Effect of ω-Conotoxins in a Pain Model

[0086] Analgesic activity of ω-conotoxins is also tested in pain models as follows.

[0087] Persistent pain (formalin test). Intrathecal (it) drug injections are performed as described by Hylden and Wilcox (1980). An ω-conopeptide or vehicle is administered in a volume of 5 l. Fifteen minutes after the i.t. injection, the right hindpaw is injected with 20 l of 5% formalin. Animals are placed in clear plexiglass cylinders backed by mirrors to facilitate observation. Animals are closely observed for 2 minutes per 5 minute period, and the amount of time the animal spent licking the injected paw is recorded in this manner for a total of 45-50 minutes. Results are expressed as licking time in seconds per five minutes. At the end of the experiment, all animals are placed on an accelerating rotorod and the latency to first fall was recorded. ω-Conopeptides are found to be active in this model which is predictive of efficacy for treating neuropathic pain.

[0088] Acute pain (tail-flick). An ω-conopeptide or saline is administered intrathecally (i.t.) according to the method of Hylden and Wilcox (1980) in a constant volume of 5 µl. Mice are gently wrapped in a towel with the tail exposed. At various time-points following the i.t. injection, the tail is dipped in a water bath maintained at 54 C. and the time to a vigorous tail withdrawal is recorded. If there is no withdrawal by 8 seconds, the tail is removed to avoid tissue damage.

[0089] Neuropathic pain. The partial sciatic nerve ligation model is used to assess the efficacy of Mar1 in neuropathic pain. Nerve injury is produced according to the methods of Malmberg and Basbaum (1998). Animals are anesthetized with a ketamine/xylazine solution, the sciatic nerve is exposed and tightly ligated with 8-0 silk suture around 1/3 to ½ of the nerve. In sham-operated mice the nerve is exposed, but not ligated. Animals are allowed to recover for at least 1 week before testing is performed. On the testing day, mice are placed in plexiglass cylinders on a wire mesh frame and allowed to habituate for at least 60 minutes. Mechanical allodynia is assessed with calibrated von Frey filaments using the up-down method as described by Chaplan et al. (1994), and the 50% withdrawal threshold is calculated. Animals that did not respond to any of the filaments in the series are assigned a maximal value of 3.6 grams, which is the filament that typically lifted the hindlimb without bending, and corresponds to approximately 1/10 the animal's body weight.

[0090] The data obtained demonstrate that ω-conopeptides have potent analgesic properties in three commonly used models of pain: acute, persistent/inflammatory and neuropathic pain models.

EXAMPLE 8

Calcium-Channel Antagonist Activity: Inhibition of Ionic Currents

[0091] Ionic currents through calcium channels are examined in cells that are voltage-clamped by a single patch-clamp electrode. These whole-cell patch-clamp studies are performed mainly on N1E115 mouse neuroblastoma cells, although a variety of cell types, including human neuroblastoma cell line IMR-32, are also examined.

[0092] Most measurements are obtained using a bath saline that allowed examination of the calcium currents in the absence of other ionic currents. These solutions contained 80 mM NMDG (as a sodium replacement), 30 mM TEACl (to block potassium currents), 10 mM $BaCl_2$ (as a charge-carrier through the calcium channels), and 10 mM HEPES at pH 7.3. Some solutions also contained 2 mM quinidine (to block potassium currents) and 3 μM tetrodotoxin (to block sodium currents). Normal bath saline is (mM): 140 NaCl, 10 glucose, 3 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 10 mM HEPES pH 7.3. Intracellular solutions contained (mM): 150 CsCl, 0.5 $CaCl_2$, 5 EGTA, 5 $MgCl_2$, 2 K_2ATP at pH 7.3-7.4. Bath saline and all internal solutions are filtered before use.

[0093] Pipets are made from Corning 7052 glass (Garner Glass Company, Claremont, Calif. 91711), coated with Sylgard (Dow Corning, Midland, Mich. 48640) and fire-polished before use. Bubble numbers are typically 5 to 6, with pipet resistances typically 2-5 MOhms. Corning 8161, Kimble, and other glasses are also used without noticeable effect on the calcium currents observed.

[0094] Recordings are carried out at room temperature with an Axopatch 1-C amplifier (Axon Instruments, Foster City, Calif. 94404) and analyzed with pCLAMP software (Axon Instruments). Data are filtered at 1000 Hz for a typical sampling rate of 0.1 kHz; in all cases data are filtered at a frequency at most 1/5 of the sampling rate to avoid biasing. Data are collected on-line by the software. Analysis is performed on-screen with print-out via a Hewlett-Packard LaserJet Printer (Hewlett-Packard, Palo Alto, Calif. 94306).

[0095] The typical experiment is conducted as follows: after seal formation followed by series resistance compensation and capacitative transient cancellation, a voltage clamp protocol

is performed wherein the cell potential is stepped from the holding potential (typically -100 mV) to test potentials that ranged from -60 mV to +20 mV in 10 mV increments. The cell is held at the holding potential for 5 seconds between pulses. Protocols starting from other holding potentials usually covered the same range of test potentials. ω-Conopeptides are found to have calcium channel blocking activity in such cell lines.

[0096] It will be appreciated that the methods and compositions of the instant invention can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent to the artisan that other embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

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